AMERICAN SOCIETY OF CLINICAL ONCOLOGY

2015 EDUCATIONAL BOOK

"Illumination & Innovation: Transforming Data into Learning"

A PEER-REVIEWED, INDEXED PUBLICATION

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American Society of Clinical Oncology Educational Book

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The *2015 ASCO Educational Book* is published online at asco.org/edbook. Articles can also be accessed from the Attendee Resource Center at am.asco.org/ARC. Articles that are included in this print edition include a page number reference in the table of contents.

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2015 ASCO Annual Meeting Disclosure

ASCO's commitment to balance, objectivity, and scientific rigor has been reflected in its responsible management of financial interactions with for-profit health care companies that could create real or perceived conflicts of interest. To help attendees, faculty, and the Society continue to manage these interactions appropriately, ASCO has updated its conflict of interest policy and launched a new Conflict of Interest Disclosure Management System.

In the past, disclosures applied to individual activities and separate forms were completed for each one. With the updated policy and new disclosure management system, one disclosure will apply to all activities. Members and participants in activities will use coi.asco.org to disclose all interactions with companies; this disclosure will be kept on file and can be confirmed or updated with each new activity.

The full ASCO Policy for Relationships with Companies and frequently asked questions are available at asco.org/rwc. Please email coi@asco.org with specific questions or concerns.

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   Memory of Willie Tichenor*

Letter from the Editor

On behalf of my Associate Editor, Dr. Nate Pennell, I welcome you to the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting. It is my heartfelt privilege as well to present to you the 35th volume of the NLM-indexed *ASCO Educational Book*. The theme of the 2015 Annual Meeting is "Illumination and Innovation: Transforming Data into Learning." The Cancer Education Committee, helmed by Dr. John Vernon Cox, has assembled a comprehensive education program that illustrates how creative transformation of data into knowledge, and knowledge into learning, can change the lives of our patients in a sustainable and scalable manner.

Long after the halls of McCormick Place have emptied and the echoes of our colleagues' lectures have faded from our ears, the 2015 *ASCO Educational Book* will remain as an enduring source of this shared knowledge. We are indebted to the over 100 authors who generously took the time to write and, in some cases, revise, the articles in this volume. In addition, I want to recognize our truly remarkable volunteer peer reviewers who dedicated their time and effort to careful, thorough, and thoughtful reviews. I strongly believe this collaborative effort has resulted in articles that are not only highly informative, but worthy of indexing in the National Library of Medicine. Thank you for your efforts and for your commitment to education and ASCO's mission. Special thanks also go out to Lindsay Pickell at ASCO, for whom none of this could ever have been put together.

In the spirit of this year's theme, Nate and I have included in this printed volume a curated selection of articles that most embody the transformative power of data into learning. As with the 2014 *ASCO Educational Book*, this edition includes invited articles from thought leaders who played leadership roles in ASCO's many thematic and specially focused meetings. Each invited author was tasked with bringing forward an article that represented their area of oncology and also spoke to one of the major themes of the 2015 Annual Meeting. I am proud to say each author delivered high-caliber work that will stand as a major contribution to the field of oncology.

It is our honor to invite you to read through the exceptional contributions that comprise the 2015 volume, only a selection of which are found in the print edition. For access to all of the 2015 *ASCO Educational Book* articles, as well as access to past volumes, please visit www.asco.org/edbook.

Nate and I welcome your feedback and suggestions on how we can improve the content, so please contact us at edbook@asco.org with your comments.

Don S. Dizon, MD
Editor

INVITED ARTICLES

This year's invited articles come from a few of the many oncology thought leaders who played leadership roles in ASCO's thematic and specially focused meetings during 2014 and early 2015. These articles represent each author's oncology specialty as it relates to one or more of the major themes of the 2015 ASCO Annual Meeting. Articles cover topics such as big data, clinical trials, value from the perspective of the patient, value from the perspective of the institute/national policy, geriatrics, and quality, and ethics.

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The Changing Landscape of Phase I Trials in Oncology

Kit Man Wong, MD, Anna Capasso, MD, and S. Gail Eckhardt, MD

There has been an exponential rise in the number of novel anticancer drugs in development over the last decade. Our improved understanding of the molecular mechanisms of tumorigenesis has driven the discovery of molecularly targeted agents (MTAs) that inhibit specific proteins or pathways. However, although over 750 anticancer drugs are presently in development,[1] only 5% of these ultimately demonstrate sufficient efficacy for regulatory approval and clinical application.[2] For example, from 1998 to 2014, the failure-to-success ratio of investigational agents for melanoma was 14:1, whereas only 10 of 177 agents for lung cancer were approved.[3] Furthermore, the drug developmental process in oncology is estimated to take 1.5 years longer than in other diseases.[4] This highlights the need to maximize the efficiency and cost-effectiveness of early clinical trials, given the vast resources and time involved.

A phase I trial represents the critical transition of a novel compound from the preclinical to clinical stage, and thus provides the foundation for an efficacious drug development program. Several aspects of phase I trials have evolved in the era of MTAs that span multiple facets, from the overarching goals of phase I studies to trial design and the regulatory process, with consequent implications for participating institutions and investigators. This article summarizes the changing landscape of phase I trials in oncology, new challenges, and future directions.

TRIAL DESIGN

The conventional goals of phase I trials are to characterize the safety, tolerability, and maximum tolerated dose (MTD) of a novel agent by enrolling patients with a wide range of advanced cancers refractory to standard therapy. With the emergence of MTAs, new approaches related to dose escalation, patient selection, and study endpoints are making their way into current phase I studies.

Dose Escalation

The classic 3 + 3 design is a simple algorithmic method consisting of a set of predefined dose escalation rules based on the observed rate of dose-limiting toxicities (DLTs) within a specified window of assessment, typically 28 to 30 days. This approach enrolls cohorts of three patients at each dose level based on an algorithm (Table 1). The MTD is defined as the dose level at which the DLT rate is less than 33% and is usually the recommended phase II dose (RP2D) for further study. This design is well suited for cytotoxic agents, which are characterized by a positive correlation between dose, toxicity, and efficacy, and the highest dose with acceptable toxicity is desired.[5]

Although the 3 + 3 design is simple to implement, it may lead to suboptimal treatment in a large number of patients.[6] The estimated MTD may be imprecise because of the small cohort size and the nature of a rule-based approach.[7] Furthermore, MTAs may demonstrate delayed or cumulative mechanism-based toxicities that are not captured within the DLT assessment window. In these cases, the maximally administered dose is determined instead of the MTD.[6] In a systematic review of more than 450 phase I trials, the MTD was identified for 64% of MTAs compared with 99% of cytotoxic agents.[8] It is estimated that 20% of dose reductions with MTAs occur beyond cycle 1, the usual DLT assessment period.[9] Indeed, there is great heterogeneity in the DLT definition across published phase I trials of MTAs, particularly with respect to the window of assessment and severity.[10] In fact, the RP2D of MTAs should incorporate toxicity data from all cycles of therapy and symptomatic grade 2 toxicities.[9,11]

New strategies for dose escalation were developed to address these issues, including accelerated titration and model-based designs (Table 1). The accelerated titration design (ATD) as originally proposed consists of an accelerated phase of 100% dose escalation steps in successive single-patient cohorts, until DLT or substantial toxicity occurs during any cycle, at which point the trial reverts to the standard

3 + 3 scheme with smaller dose increments.[12] Not only does the ATD enable faster dose escalation without increased toxicity, it also allows more patients to be treated at the therapeutic dose.[12,13]

Model-based adaptive designs were devised to capture delayed toxicities without prolonging patient accrual. The continual reassessment method (CRM) requires a priori estimation of the dose-toxicity model, which is continuously updated by incorporating the cumulative toxicity data from all treated patients to compute the optimal dose for the next cohort.[5,14] Therefore, late onset toxicities are considered in subsequent dose level determinations. Several modifications have been made to the original CRM to further enhance safety or flexibility, such as sequencing 3 + 3 and CRM,[15] the quasi-CRM for nondichotomized toxicity grades,[16] the time-to-event CRM for very late toxicities as observed postradiation,[17] and other extensions to handle subject heterogeneity or varying treatment schedules.[18] Although the CRM is advocated, it requires a close collaboration between the investigator and biostatistician throughout the dose escalation phase.

The efficiency of novel dose escalation designs was demonstrated in a study of 84 phase I trials from 2000 to 2010. Compared with the traditional strategy, new designs explored a greater number of dose levels (median of 6, 8, and 10 levels for 3 + 3, ATD, and modified CRM, respectively) and achieved a higher mean MTD-to-starting dose ratio (ratios of 9, 22, and 30, respectively).[19]

The changes in dose escalation in phase I trials have resulted in fewer patients enrolled per dose level. This presents a challenge to multi-institutional studies, as individual sites

enroll very few patients, not only preventing investigators from gaining adequate experience with a drug and its toxicities, but also limiting the number of patients sampled for pharmacokinetic (PK) and pharmacodynamic (PD) studies. Greater communication between sites also is necessary to completely capture the toxicity data for dose escalation decisions. Therefore, in some respects, the multisite nature of current phase I trials may drive the continued use of more traditional designs.

Patient Selection

Rather than a single dominant gene, it is now recognized that most cancers arise from multiple somatically mutated oncogenes, each contributing a small effect, which accumulate during tumor progression. Thus, even within the same cancer type, individual tumors are driven by distinct sets of genes and pathways.[20] It is this genetic heterogeneity that underlies the observed variable responses to MTAs.

In most cases, an MTA is active only in a subgroup of patients who may be identified using predictive biomarkers, such as the expression level of a gene or protein, or the presence of a gene mutation, amplification, or translocation. Phase I trials increasingly are used as a platform to explore biomarkers and enrich molecular subsets of patients most likely to respond to specific MTAs. When used appropriately, this can improve the efficiency and safety of drug development.[21] For instance, the successful use of biomarker-driven patient selection was exemplified by the phase I trials of crizotinib (PF-02341066) in EML4-ALK rearranged non-small cell lung cancer[22] and vemurafenib (PLX4032) in BRAF V600E mutant melanoma,[23] in which the remarkable responses in these patient subsets helped to accelerate their approval.

However, challenges are inherent in incorporating biomarkers in early drug development.[5] As most cancers have multiple genetic aberrations, sensitivity to an MTA is likely modulated by many factors. Also, identifying a reliable biomarker may be less feasible when an agent has several targets, as is the case with most tyrosine kinase inhibitors. Since the misapplication of predictive biomarkers can potentially be over-restrictive and exclude patients who might benefit from an MTA, establishing a very strong scientific basis for the biomarker with preclinical validation is a prerequisite, as is acceptable sample collection, assay performance, reproducibility, and standardization.[24-28] For these reasons, biomarkers typically are investigated as exploratory objectives.

The increasing use of biomarker-based patient selection has transformed the enrollment process of phase I trials. First, patients must be molecularly screened to determine their eligibility. Where the biomarker of interest has a low prevalence, many patients must be screened to identify a few potential candidates, and more studies have to open at a single center to accommodate all patients wishing to enter a trial. Phase I teams must be highly organized to obtain archival tissue or fresh biopsies in a timely manner and be prepared to manage patient anxiety from invasive screening procedures and negative results. Furthermore, since many

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KEY POINTS

- Several aspects of phase I trials have evolved in the current era of molecular targeted agents to adapt to the changing nature of anticancer therapy and to increase the efficiency of drug development.
- Current phase I designs are increasingly integrating novel dose-escalation approaches and biomarker-driven selection of patients, as well as expanding study objectives to include the evaluation of efficacy and pharmacodynamics/pharmacokinetics in addition to safety.
- Changes to the regulatory approval process have helped to expedite drug development, particularly for novel agents with a strong biologic rationale and proof of concept, validated predictive biomarker, and clear evidence of efficacy in early trials.
- As a result of the substantial changes in phase I trial goals and conduct, there is a parallel shift toward multi-institutional trials and central study management by clinical research organizations.
- The use of multi-institutional trials has a significant impact on the structure of phase I programs and the experience of investigators, particularly because of limited patient enrollment at each site.

Table 1. Comparison of Dose Escalation Designs

	Algorithmic Design (3 + 3)	Accelerated Titration Design	Model-Based Design (Continual Reassessment Method)
Dose levels	Predefined starting dose level (considered safe in humans based on data from animal models) and DE steps	Predefined starting dose level (considered safe in humans based on data from animal models); DE steps determined by occurrence of DLT	Starting dose level based on a prior dose-toxicity curve and target DLT rate; dose of next cohort determined by the updated model using the same target DLT rate
Number of patients per cohort	3 patients in each cohort; 6 patients in an expanded cohort	1 patient in each cohort during the accelerated titration phase; 3 or 6 patients in each cohort once DE reverts to standard 3 + 3	Number specified by the investigator, typically 2 patients per cohort
DE scheme	Patients are enrolled (3 at a time) in each successive cohort. When 1 out of 3 patients has DLT, the cohort is expanded to 3 more patients at the same dose level. If 2 or 3 patients in a cohort have DLTs, the next lower dose level is expanded to 3 more patients.	During the accelerated phase, DE steps occur at 100% increments until one DLT or two moderate toxicities occur at any cycle. Then, DE reverts to the standard 3 + 3 design with 40% DE steps.	The dose-toxicity model is updated on an ongoing basis using the cumulative toxicity rate from all previously treated patients to determine the optimal dose level of the next cohort using the same target DLT rate
MTD	Dose level at which there is ≤ 1 DLT out of 6 patients (< 33%)	Dose level at which there is ≤ 1 DLT out of 6 patients (< 33%)	Dose corresponding to the predefined target DLT rate based on the final updated model
Advantages	- Simple, easy to implement	- More patients treated at the therapeutic dose	- More patients treated at the therapeutic dose
	- Does not require statistical modeling	- Faster DE and MTD reached with the same number of patients	- Model-based approach allows more accurate estimation of MTD
	- Allows conservative DE for drugs with narrow therapeutic index		- Takes into account delayed toxicities
Disadvantages	- Many patients may be treated at subtherapeutic doses	- May not be appropriate for agents with narrow therapeutic index	- Continual modeling by a biostatistician is needed
	- MTD may be imprecise		
	- May not be appropriate for MTAs with no or delayed toxicities		

Abbreviations: DE, dose escalation; DLT, dose-limiting toxicity; MTA, molecularly targeted agent; MTD, maximum tolerated dose.

biomarkers are disease-specific, centers must be able to rapidly screen large numbers of patients for disease-specific expansion cohorts, which may pose a challenge when the phase I program is not well integrated with subspecialty clinics. Finally, each patient in need of an experimental therapy has to be considered for multiple studies at the same time to avoid delays in entering a trial in the event of a screen fail. Strategies to facilitate the inclusion of molecularly selected patients are needed, such as molecular prescreening programs for all metastatic patients to ease the transition to a phase I trial on disease progression.[29]

Endpoints

The conventional primary endpoint of phase I trials has been toxicity, with efficacy as only a secondary outcome. However, with the new breakthrough therapy designation created by the U.S. Food and Drug Administration (FDA) to expedite drug development, obtaining early evidence of efficacy is now an important component of phase I studies. This has increased the use of tumor-specific expansion cohorts to further characterize both safety and clinical response at the RP2D,[30] which is associated with a higher success rate of phase II trials and faster drug approval.[31] As mentioned above, the organization of some phase I centers also has been restructured around disease-specific investigators and clinics.

Moreover, in the MTA setting, the use of toxicity as the primary determinant of the RP2D has been called into question.[32] Unlike cytotoxic agents, the efficacy of MTAs may not be reliably predicted by either dose or toxicity. Increasingly recognized for MTAs are mechanism-based toxicities that relate to the presence of the target on normal tissues and cause chronic toxicities.[33] Although not always dose-limiting, the latter may nonetheless be compliance-limiting (e.g., rash, diarrhea, fatigue). These and other physiological adverse effects of MTAs (e.g., hypothyroidism, hypertension) require the parallel development of supportive care regimens and collaboration with other medical specialists for optimal clinical development.[34-37]

For MTAs, alternate endpoints reflecting target modulation may be more relevant surrogates of efficacy when determining the RP2D, and they may assist in prioritizing drug candidates for further development.[38] Therefore, the PD analysis of MTAs has become an integral part of phase I trials. Common correlative endpoints include protein expression in tumor tissue by immunohistochemistry before and after treatment, which requires invasive tissue acquisition procedures, as well as less invasive assays of serum proteins, peripheral blood mononuclear cells, and imaging biomarkers.[5,6] Circulating tumor cells and DNA will likely play an important role in the future as liquid biopsies.[39,40] Moreover, PK endpoints are often simultaneously analyzed to charac-

terize the PK-PD and PK-toxicity relationships, which can guide the selection of the RP2D when the plasma drug concentration for maximal biologic effects is known.[32,41] Well-planned correlative endpoints can significantly improve the efficiency of drug development and reduce overall costs.[38]

Therefore, although the evaluation of safety remains the primary goal of early phase studies, assessment of efficacy and PD/PKs also are key objectives in this new era of drug development. This, in turn, is transforming the landscape of phase I trials, with greater emphasis on disease-focused clinicians, tissue acquisition and assay performance, multidisciplinary supportive care, and radiological expertise in functional imaging.

REGULATORY CHANGES

The development of a successful drug from first-in-human study to approval normally takes about 7 years, during which its safety and efficacy are thoroughly and rigorously assessed.[42] However, in the case of MTAs with a clearly established biologic mechanism backed by proof of concept, unprecedented clinical responses with minimal toxicity, and availability of a strong predictive biomarker, many argue that the approval process should be shortened, especially when promising results are observed in early phase. Strategies to expedite drug development were proposed in the FDA Safety and Innovation Act of 2012. Thus, the new breakthrough therapy designation for investigational drugs was added to FDA's armamentarium of programs that also include the fast-track designation, accelerated approval pathway, and priority-review designation (Table 2).[43]

The opportunity to exploit such pathways has a substantial effect on phase I trial conduct. Not only are efficacy end-points emphasized in the design, the quality of data is increasingly scrutinized because it may be used for a new drug application. In fact, trials frequently are now managed by large clinical research organizations (CROs) to standardize trial conduct and data collection.

PRACTICAL IMPLICATIONS

Over the past decade, phase I trials have evolved from single-/oligo-site studies to increasingly large multi-institutional efforts with the goal of expediting patient accrual. In the latter, three or more institutions typically enroll patients, and slots in each cohort are assigned by the sponsor or filled on a competitive first-come first-served basis.

Multi-institutional trials have several implications, including limited slot availability per site, thus requiring more trials to be opened at a center to accommodate the same number of patients. Moreover, additional staff, resources, and frequent conference calls among participating sites are needed to enable real-time notification of adverse events and DLTs. These factors have led to greater reliance on CROs for study management. Further, the desire to accelerate patient recruitment results in the selection of sites based on their ability to enroll rather than on the experience and quality of the phase I program.

Similarly, the experience of phase I investigators has been influenced by multi-institutional trials. An individual investigator at one site can only gain limited clinical experience with a novel agent and its spectrum of toxicities.[8] Moreover, since sponsors and/or CROs are usually responsible for overseeing the operations of current phase I trials, it is a challenge for trainees and junior faculty to obtain comprehensive training in early drug development. Consequently, many years

Table 2. Main Features of the FDA's Expedited Programs for Serious Conditions

	Qualifying Criteria	Features
Fast track designation	A drug that is intended to treat a serious condition AND nonclinical or clinical data demonstrate the potential to address unmet medical need	- Actions to expedite development and review
		- Rolling review
Breakthrough therapy designation	A drug that is intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on clinically significant endpoint(s) over available therapies	- Intensive guidance on efficient drug development
		- Organizational commitment
		- Rolling review
		- Other actions to expedite review
Accelerated approval pathway	A drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than IMM that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)	- Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit
Priority review designation	An application (original or efficacy supplement) for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness	- Shorter time for review of marketing application (6 months compared with the 10-month standard review)

Abbreviations: FDA, U.S. Food and Drug Administration; IMM, irreversible morbidity or mortality.
Adapted from: U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for industry: expedited programs for serious conditions-drugs and biologics. May 2014. www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. Accessed December 27, 2014.

of experience may be required before they are fully competent in designing and carrying out phase I studies, highlighting the importance of strong mentorship in this setting. At the same time, it has become more difficult for junior faculty to be truly independent investigators of phase I trials and advance their academic careers. This is especially true at smaller centers that lack the capacity to compete for enrollment. Therefore, although multisite trials have the advantage of improving efficiency, these issues have led some to suggest that no more than three centers participate.[5]

CONCLUSION

Phase I trials are the cornerstone of developmental therapeutics, and they are playing an expanding role in the changing landscape of cancer drug development. In the era of MTAs, they have evolved into complex studies that provide much more information than merely safety. With different dose es-

calation designs, molecular patient selection, and alternate endpoints, not only can current well-designed phase I trials better determine the RP2D of an MTA, they can also provide an opportunity to demonstrate proof of concept, characterize PD/PKs, define predictive biomarkers, and explore early efficacy that may potentially expedite drug approval. Importantly, this has led to a shift toward multi-institutional trials and CROs, greater demand on individual sites in terms of patient screening and enrollment, and the need to open more studies at each center.

Coupled with FDA initiatives to accelerate drug approval, current phase I studies can greatly advance the drug development process, as evidenced by the success of recently approved MTAs. In fact, the landscape of phase I oncology trials is ever-changing. As we continue to discover new molecular targets and better therapies, phase I trials must continue to evolve to efficiently translate these innovative therapies from bench to bedside.

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Genomics, Personalized Medicine, and Supportive Cancer Care

Stephen T. Sonis, DMD, DMSc

The successes of the Human Genome Project catalyzed the transition of genomics from the laboratory to the clinic. Over the past decade, there has been a proliferation of studies demonstrating the potential utility of various applications of genomics as a conduit to accelerate drug development, understand mechanism(s) of action, and personalize treatment. For patients with cancer, genomics-informed medicine has largely focused on issues associated with patients' malignancies. But with the recognition that genomics is also a pivotal contributor to risk of regimen-related toxicities and how patients respond to treatment, the chances for applying genomics to comprehensive cancer care are increasing.

BACKGROUND

The application of genomics as a tool to personalize cancer care is not new. Headlines about individualizing oncology treatment have been heralded in both the lay and scientific press. The use of *Oncotype* DX to predict the course and guide treatment of early estrogen-receptor positive breast cancers has made its way into both the American Society of Clinical Oncology and National Comprehensive Cancer Network guidelines.[1,2] However, individualized cancer care based on genomics is still only having a marginal effect on the vast majority of oncology patients. Although the emphasis of oncologic-associated genomics primarily has focused on defining tumor risk, biology, and response, the potential opportunities associated with the application of genomics to supportive cancer care are just evolving.

Few patients avoid toxicities and side effects of cytotoxic and targeted anticancer regimens. The list of complications is extensive and diverse. Treatment can result in specific tissue injury (e.g., mucositis, pneumonitis, dermatitis, diarrhea, nausea and vomiting, and neuropathy) or more generalized consequences (e.g., fatigue, cognitive dysfunction, and cachexia). As every oncologist has observed, not all patients are equally threatened for specific treatment-related side effects. Although overall risk is, to some degree, associated with regimen selection, drug or radiation dose, and route of admin-

istration, patient-centric variables are major contributors. Why do two patients of the same sex, same weight, with the same malignancy, and treated with the same drug regimen differ so significantly in their response? It continues to become increasing clear that genomics play a pivotal role in determining an individual's risk of developing adverse responses to chemotherapy or radiation therapy.

The ultimate objective of therapy is the eradication of primary and secondary disease with as little collateral damage (toxicity) as possible. In fact, data suggest that patients overwhelmingly indicate a tolerance for a risk of treatment side effects in favor of a better chance of tumor cure.[3] However, it is also becoming more evident that there is a point at which the extent and nature of the toxicity risk tips patient decision making in favor of less aggressive cancer therapy. Furthermore, as we respond to patients' desire to be involved in treatment choices, we must provide information on the projected efficacy of regimen options and the probability of associated toxicities.[4]

Pharmacogenomics offer providers and patients individualized outputs that describe a comprehensive assessment of the likelihood of both treatment success and the specific probability of specific toxicities. Data from recent studies confirm that patients are overwhelmingly supportive of genetic testing that provides meaningful information about tumor response and toxicity risk.[5] These results, however, also demonstrate substantial gaps in patient and provider perceptions of treatment complication effects and how information is conveyed about toxicities.

Do patients really understand what they are getting into with toxicities? It is hard to believe that patient decision making around toxicity tolerance would not be colored if they better understood the differential ramifications of acute and chronic toxicities, if they were aware of toxicity treatment options, or if they were able to appreciate their individual risk for specific side effects. Data gathered from women with breast and ovarian cancers indicate[6,7] a huge variance in how patients weigh side effects. Nausea and vomiting, sensory neuropathy, and mucositis are examples of least acceptable side effects, whereas alopecia and fatigue seem to be most acceptable. Im-

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portantly, patients were able to make treatment preference decisions based on their understanding of toxicity risk within the context of cancer therapy treatment outcomes.

From the standpoint of integrating genomics into a comprehensive management paradigm that includes supportive care, a genomic test that addresses the inclusive risks of toxicities has most value when it is interpreted in the context of a specific anticancer regimen. For example, if a patient with breast cancer can be effectively treated for her disease with either Regimen A or Regimen B and the risk of the toxicity profile associated with each regimen can be defined, the patient and the oncologist can choose one over the other based on patient preference. If, on the other hand, Regimen A is not as effective as Regimen B, but the toxicity risk profile is more tolerable to the patient, there may be a trade-off point at which the patient determines that the risk and scope of side effects outweigh the selection of the potentially more effective cancer treatment.

A second value in understanding a patient's toxicity risk focuses on the chance to individualize and target the use of medications that prevent or treat specific side effects. For example, approximately 40% of patients treated with certain conditioning regimens for hematopoietic stem cell transplant develop severe oral mucositis with all of its consequent comorbidities. Palifermin, keratinocyte growth factor-1, is approved to prevent its development.[8] To be effective, palifermin must be administered for 3 days before the infusion of the conditioning regimen, a time in which there is no evidence of mucosal injury. Not only does this schedule add days to care, it also incurs substantial financial costs. Both are well worth the price for the individual at risk of mucositis, but there is more to be lost than gained for the remaining 60% of patients. Thus to administer palifermin to everyone does not make sense at multiple levels. However, if one could predict with reasonable certainty which patients were at risk for developing mucositis, the agent could be given selectively and more economically.

In addition to risk prediction, at least two other potential applications for genomics as it relates to personalization of supportive cancer care are available. In the current paradigm of drug development, success or failure is defined as an assessment of the mean.[9] Criteria for efficacy are set around a one-size-fits-all vision in which it is presumed that all patients have an equivalent response to a drug. Since the response rate for drugs ranges dramatically (90% of drugs work in only 30% to 50% of patients),[10] we know this is not the case. There is clearly individuality in how any population with cancer responds to a drug. Clinicians often deal with this variance by adjusting dose or through trial and error. However, genomic differences often define response/nonresponse and the ability to dichotomize patients prospectively offers a great opportunity to personalize their care and create hierarchies for toxicity intervention. For example, if multiple agents to treat chemotherapy-induced nausea and vomiting are available, knowing which one was most active in a prospective patient makes prescribing more efficient and cost-effective.

Finally, genomics provides an important tool in drug development— discovery through clinical trials. Both radiation and chemotherapy stimulate changes in gene expression that trigger the pathobiologic events that produce toxicities. Identifying and defining the sequence of gene activation that underlies regimen-related injury provides specific targets for intervention. In addition, by mapping the inter-relationships between cooperative groups of genes and organizing these into networks, the hubs at the center of the network can be targeted and disrupted. This approach mimics what happens to the United Airlines flight schedule when there's a snowstorm in Chicago.

PHARMACOGENOMICS AND TOXICITY-RISK PREDICTION AND TREATMENT
Pharmacokinetic Risk Assessment

Genomic contribution to chemotherapy-associated toxicity risk is governed by two components: one associated with the concentration and availability of the drug (pharmacokinetics [PK]), and the other on how the drug affects the biology that underlies the pathogenesis of the toxicity. Drug dosing typically is determined on a one-size-fits-all notion (recommended dose) that typically has been determined by dose escalation in clinical trials based on the mean response of the study population. Although dosing is adjusted based on patient size, variable efficacy and toxicity outcomes are common. This should not be a surprise because we now know that patients do not handle drugs in a uniform way. Drug metabolism is affected by enzymes, and enzymes are controlled by genes. Too much enzyme production and the drug's tumoricidal effects are minimized, but toxicity risk is low. Too little enzyme production and there is an effective overdose with a large toxicity risk.

A classic example of a PK-related pharmacogenomic marker of toxicity-risk prediction is the catabolic enzyme, dihydropyrimidine dehydrogenase (DPD), which plays a critical role in fluorouracil (5-FU) metabolism.[11] Insufficient DPD activity results in toxic levels of 5-FU and is associated with increases in both hematologic and nonhematologic toxicities. Variants in the *DPYD* gene affect DPD activity. At least two variants, DPYD*2A and D949V,[12] have been identified, largely through a candidate gene approach, as being associated with increased toxicity risk. Furthermore, additional DPYD variants have been uniquely described in black patients, a finding that emphasizes the importance of broad demographic inclusion criteria in any study aimed at identifying genes affecting PK.[13] DPD currently is the only genomic marker for 5-FU risk prediction that the U.S. Food and Drug Administration (FDA) recognizes and for which a commercial test exists.[14] Not surprisingly, not all tests have equivalent value.[15]

An association between gene-based changes, pharmacokinetics, and toxicity risk also has been described for many chemotherapeutic agents,[16] including methotrexate, platinum drugs, taxanes, and anthracyclines.[17-19] Results of these studies have been largely inconsistent. Whether the variance in findings is a consequence of small sample size, inconsistent study design, differences in candidate gene or SNP selection, or variability in toxicity definitions is unclear. But the disparity in conclusions is remarkable. For example, two studies of the genomic PK toxicity association in pediatric patients

treated with methotrexate for acute lymphoblastic leukemia (ALL) reached totally different conclusions. Den Hoed et al[20] found no association between either methotrexate (MTX) levels or single nucleotide polymorhphisms (SNPs) commonly associated with metabolic genes and a sentinel toxicity (mucositis). However, Csordas et al reported a link between increased MTX levels, novel metabolic genes, and acute toxicity.[21]

The majority of genomic/PK studies have two common methodological themes that might contribute to their inconsistent findings. First, they are generally based on the premise that individual genes govern PK risk, rather than considering the possibility that multiple, synergistically functioning genes may be more significant. Second, largely in concert with the previous point, they rely almost exclusively on a candidate gene or SNP approach to form a suspect list, as opposed to an open, learned method to identify genes of interest.

Although more work must be done to frame accurately the application of genomics to pharmacokinetic-associated toxicity risk, it is important to note that even in the case of DPD and 5-FU toxicity, the percentage of patients who have frank DPD deficiency does not exceed 10%, and the percentage of patients with even partial deficiencies is even less. This observation raises a critical question: How does genomics contribute to toxicity risk outside of a PK mechanism? Likewise, how can genomics assist in the prediction of radiation therapy–associated toxicities in which drug metabolism is not a consideration?

PHARMACODYNAMIC RISK ASSESSMENT

The pathogenesis of regimen-related toxicities is more biologically complex and dynamic than imagined several decades ago. The concept that tissue injury associated with chemotherapy or radiotherapy is simply the result of the indiscriminant death of rapidly dividing normal cells that has been replaced by findings detailing sequential activation of molecular and cellular pathways that mediate damage.[22] Systemic side effects of treatment have been associated with increased levels of biologic active drivers of symptoms.[23] Further, genes noted to be expressed in diseases with comparable phenotypes have been identified in patients with cancer with symptoms of diarrhea (inflammatory bowel disease), fatigue (chronic fatigue syndrome), and cognitive dysfunction (Alzheimer's).[24]

Consequently, investigators have been drawn to assess the possibility that genes that control pathways or proteins thought to be toxicity mediators could be used to predict risk. In general, two investigational approaches have been used for these studies: candidate gene/SNP protocols and genome-wide association studies. Since there have been accumulating reports indicating that inflammatory and profibrotic cytokines, and mediators of oxidative stress are implicated in the pathogenesis of regimen-related normal tissue injury, genes and SNPs associated with variations in patients' production of these proteins are among the most studied using candidate gene/SNP methodologies.

The candidate gene approach is based on targeting those genes or SNPs that have been reported to be implicated in the production of the protein of interest and linked to mecha-

nisms that lead to the toxicity of interest.[25,26] The investigator picks a gene or SNP based on prior knowledge (usually from the literature) and then tests only for them. This approach is economical, but relies highly on what is already known and presumes a one gene– one phenotype determination. Among genes or SNPs that have been implicated as risk predictors using this approach are polymorphisms for TNF,[27] TGF-beta,[28] DNA DSB repair,[29] and VEGF.[30]

Unfortunately, the results of candidate gene studies have been disappointingly difficult to validate. In a study of over 1,500 patients with breast or prostate cancer, Barnett et al were unable to validate any of the genes or SNPs reported to be associated with late toxicities of radiation therapy.[31] Why is this? The most obvious reason is that the key predictive gene or SNP was selected incorrectly. To compensate for this, some investigators have looked at panels of genes that are reportedly associated with variations in biologic activity. However, even this approach has failed to provide consistent results.

The availability of gene and especially SNP array technology led to an opportunity for a vastly more comprehensive approach, genome-wide association studies (GWAS). Genome-wide association studies allow the investigator to fish for correlations between SNPs (and associated genes) and phenotypes of interest, usually using a case-control approach in which differences in SNP expression are determined between patients who develop toxicities of interest and those who do not.[32] Associations are done in a sequential analysis between one SNP at a time and the phenotype using traditional association studies.[33] The number of SNPs available on arrays has proliferated dramatically over the past few years— current chips contain over 4 million SNPs. Given that number, the probability that some association will be discovered is extremely high. The probability is so high that conventional statistical parameters of significance are of little value. To compensate, a statistical penalty is applied to these studies, or, more recently, measures of false discovery. The need for such measures became obvious because of the high false positive rates which were typical of these studies. In addition, modest subject numbers often contributed to the high rate of false positives. Nonetheless, the literature contains a number of reports identifying SNPs predictive of regimen-related toxicities. To date, validating studies are few.

Similar to candidate gene studies, GWAS have largely been driven by the objective of trying to identify *the* gene or SNP associated with toxicity risk. These studies largely presume that the functional relationship of a SNP to a gene is critical to its potential importance as a risk predictor. It turns out that neither of these concepts optimizes the potential utility of genomic risk predictors.

Genes often act synergistically to affect function. This concept has been defined biologically by the identification of ontological and functional pathways. Furthermore, since not all genes or polymorphisms may contribute equally, a hierarchical model can be developed that helps to define contribution. Similar to a championship sports team, the clinical and biologic effect of a group of genes may be more dependent on how each member of the team contributes to the aggregate, rather than the performance of a single star. Importantly, the predictive value of the

elements of a cluster of polymorphisms is greater than the contribution of any of the contributing parts. This principle was demonstrated by Tucker et al in studies of radiation-induced pneumonitis.[34] Their evaluation of 16 polymorphisms associated with 10 genes demonstrated the increasing predictive value of multiple SNPs over fewer numbers. Additionally, although SNPs occurring outside of genes were mockingly referred to as junk DNA, it has now become evident that such polymorphisms have value, not only as effective genetic markers, but as functional modifiers.[35]

Whereas the single SNP approach suffers from its inability to identify associations because of the simultaneous presence of multiple variants in different DNA regions,[36] GWAS often identify too many associations (false positives) as a result of dependencies between SNPs in contiguous regions (linkage disequilibrium) and the dependency between SNPs on different chromosomes.[37]

Amalgamating these findings leads to the conclusion that the optimal way to identify genomic risk predictors should provide for a learned outcome in which (1) the genomic results dictate the genes or SNPs of interest, (2) there is a mechanism to filter those genes or SNPs that are extraneous without diluting the ultimate prognostic significance or pool, (3) there is a way to identify and define those polymorphisms and genes that function synergistically to contribute to risk in as precise a way as possible, and (4) there is a high degree of sensitivity and specificity. Multivariate statistical models circumvent many of the limitations noted above by examining the overall dependency structure between genotypes, phenotype, and nongenetic variables.

There is now a growing list of other analytic options that seem to meet the above criteria and seek to identify groups of SNPs or genes that are defined probabilistically by their combined ability to predict risk. We have used two analytic approaches to identify predictive gene networks or clusters. In one method, we used a Bayesian approach to identify SNP-based gene networks that were predictive of oral mucositis in autologous stem cell recipients.[38]

The first step is to whittle down the total output from a typical SNP microarray (1 to 4 million depending on the size of the array) by filtering out those SNPs that are highly unlikely to contribute to the predictive value of the Bayesian network. This is done using a simple chi-square statistic to identify the top 200,000 SNPs associated with the phenotype of interest (mucositis, in our case). Using another heuristic, the number of SNPs likely to contribute to risk differential is further filtered to identify the 4,000 SNPs from which a Bayesian network can be discovered. Unlike classical methods of identifying the important genes or SNPs based on an expression threshold, the Bayesian approach does not conduct significance tests, but ranks alternative models of association on the basis of posterior probability (to provide for inference). As such, no threshold is needed to select the most probable network. The predictive strength of the network is learned so it becomes stronger as more data are entered. As with any study of this type, a key component is testing the predictive validity of the network using an independent group of patients.

Another method that is defined by self-learning and the generation of a predictive team of genes also uses a series of statistical filters to determine the team of genes with the highest probabilistic chance of being associated with toxicity risk.[39] Like the method described above, the first sets of filters provide a large, but effective, net to capture those genes most likely to be in play and to discard those that are probably extraneous. This technique proved to be effective in identifying a group of genes that discriminated patients with prostate cancer who were at risk for radiation therapy–associated fatigue from those patients who were unlikely to be hampered with the same side effect. Then, by testing the effect of each gene on its contribution to the predictive value of the team, a highly discriminating list of predictive genes could be described.

Since most studies that generate predictive genomic endpoints are largely designed around some form of internal validation, it is imperative that an external set of subjects be tested against the prognostic criteria to assure their legitimacy.

GENOMICS AND DRUG DEVELOPMENT FOR SUPPORTIVE CARE INDICATIONS

Gene analytics can expedite the recognition of drug targets for supportive care indications. By defining the sequence and organization of genes expressed in response to chemotherapy or radiation therapy as they relate to the development of toxicity, key regulators of the process can be identified and targeted. As such, regimen-related toxicities provide substantial advantages over most chronic diseases because genomic studies that characterize the pathogenesis of cancer treatment side effects provide a baseline state at which the phenotype of interest, and presumably the genes associated with its development, are absent. The oncologist then flips the switch to start the biologic cascade that leads to the toxicity, thereby permitting investigators to sample time points leading up to, during, and after the toxicity is present. Compare that to the patient with ongoing disease (e.g., asthma, IBD, or arthritis) for whom there is never an opportunity to evaluate baseline gene expression. Performing studies in patients with an existing disease means that the malady is already ongoing when the patient first presents for evaluation. In the patient with cancer, the changes in gene expression are expressly associated with antitumor treatment and can be directly compared to levels at a time when the patient is treatment-naive.

PHARMACOGENOMIC APPLICATIONS FOR DRUG DEVELOPMENT

Once changes in gene expression are discovered following treatment, and correlated with the development of specific toxicities, questions around both toxicity pathogenesis and identification of interventional targets can be answered. Using genes selected (learned) with a Bayesian analytic algorithm, functional pathways whose differential activation best explains the differences between patients with and without the toxicity can be identified using established databases

FIGURE 1. Differentially Expressed Genes Defined by Signaling Functions
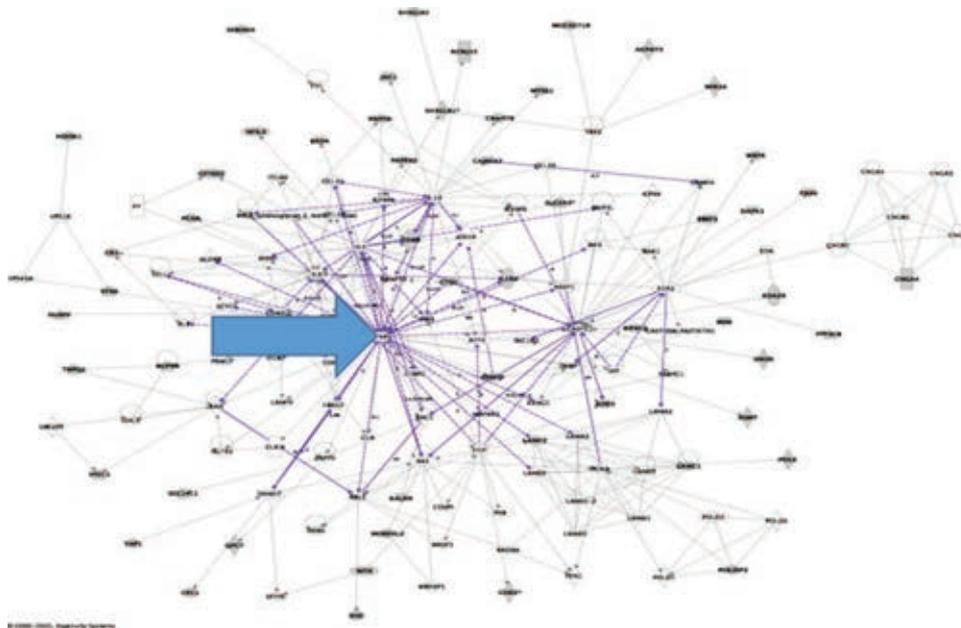
Major roles for TNF-alpha have been suggested in pathoetiology of radiation-induced toxicities, including mucositis and fatigue. The formation of a network based on differentially expressed genes in patients who developed mucositis confirms a central role for TNF, illustrates its effect on connected nodes, and provides a potential target for pharmacologically-based intervention.[40]

such as Ingenuity Pathways Analysis (Ingenuity Systems). Network analyses identify the biologic functions and canonical pathways that are most significant to the genes in the network (Fig. 1).[40]

This methodology has been used to provide an abundance of mechanistic data to define regimen-related tissue injury. Canonical pathways associated with NF-kappa B signaling, Toll-like receptor signaling, P13K/AKT signaling, interleukin-6 signaling, and p38 MAPK signaling are among examples that are consistent with proposed mechanisms by which toxicities, such as mucosal injury, occur. From the viewpoint of drug development, the key roles played by each pathway suggest that each is a potential therapeutic target.

An analysis of canonical pathways may also provide hints to the global symptomatic response of patients to cancer therapy. For example, although overexpression of genes within the glutamate signaling pathway has been associated with central nervous system activity, recent analyses suggest broadened activity, including a role as a signal mediator.[23] This conclusion has implications in drug development and might favor and inform formulation and/or route of administration strategies.

The fact that genetics can play a key role in determining a patient's response to a drug creates opportunities for both expediting drug development and individualizing care. By identifying a genetic signature that differentiates the likelihood of response or nonresponse to a drug, developers would have the ability to enrich clinical trials with groups of patients who were most likely to benefit, and, at the same time, spare genetically-defined nonresponders from the risks and inconvenience of receiving an experimental agent. Once approved, compounds that effectively mitigated regimen-related toxicities could be selectively administered to the most appropriate patients, favorably affecting the physiological and financial costs of treating nonresponders.

ECONOMIC, POLICY IMPLICATIONS, AND CHALLENGES FOR THE APPLICATION OF GENOMICS TO SUPPORTIVE CANCER CARE

For a clinical genomics test to achieve acceptability by patients, clinicians, payers, and regulators, it has to successfully answer two questions: Does it work and is it worth the cost?[41] How to answer the first question has been a topic addressed in a variety of forums. In 2004, the Centers for Disease Control and Prevention launched the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative. The group defined four evaluation criteria: analytic validity (how well does the test measure what it is supposed to measure); clinical validity (how well does the test predict its specified outcome); clinical utility (how well does the test improve or harm outcomes to patients); and ethical, legal, and social issues.[42]

In general, the efficacy of genomic tests as toxicity-risk predictors using the validity criteria cited above requires data drawn from large populations of patients. As noted earlier in this article, results of studies using either candidate gene or GWAS approaches have been notoriously difficult to replicate, and, in the case of GWAS, prone to false-positive signals. Fortunately new big data methods and the integration of multifaceted analytics provide a platform from which genomic parameters with toxicity risk can be determined. Based on past experiences, such studies likely will be most effective if they are prospective and if they provide a strict template for the capture of accurate toxicity data.

Defining the clinical utility of a genomic test in the context of supportive care may turn out to be complex. Toxicities rarely occur as singular events. Rather, patients develop simultaneous clusters of toxicities[43] often related by common biologic underpinnings. This may be advantageous from the potential of testing because there may be pathways (and genes) that are shared by more than one toxicity. Compartmentalizing genomic risk testing (i.e., toxicity by toxicity) ultimately is less attractive than a comprehensive toxicity panel, especially with respect to adding meaningful information for clinician-patient decision making. A test's true utility will be derived from cases in which patients can select equally effective anticancer regimens based on their toxicity preferences.

Economics play an increasing role in health care decision making today. Aside from patients, health economic stakeholders include providers, payers, and government. It initially appears that a sound fiscal argument can be developed in favor of genomic testing for supportive care indications, as long as it results in an actionable outcome that affects toxicity risk, prevention, or effective management. Numerous studies have demonstrated increased costs and increased health resource use attributable to specific toxicities.[44,45] However, these data might be underestimates. In many cases, only severe forms of adverse events have been evaluated, even though it is likely that toxicity of any grade affects cost.[46] The incremental financial effect of toxicities has also been differentially described for direct costs (those costs associated with the costs of managing the toxicity) or indirect costs (lost opportunity costs, caregiver costs, etc.). For the most part, direct costs have been delineated for acute toxicities, whereas indirect costs are often attributed to chronic adverse events (i.e., the effect of cancer treatment–related fatigue on inability to return to work).

As noted above, the finding that patients most often develop multiple, simultaneous toxicities mandates that true cost assessment be done in a comprehensive way, rather than toxicity by toxicity. It also places an obligation to develop genomic assessments that, in a single test, capture comprehensive toxicity risk and link those to alternative regimens for the same cancer. The recent report by Hurvitz et al[47] of a large number of patients with metastatic breast cancer provides a rationale for such an approach. Using an extensive claims database, they first identified the 22 most common adverse events associated with common chemotherapy regimens. They computed and compared the comprehensive monthly costs per number of adverse events. The results were dramatic. Increases in average monthly costs ranged from $854 to $5,320 depending on chemotherapy regimen.

Consequently, even considering the additional costs of testing (including test development), the prospective identification of risk that results in the avoidance of toxicity either by guiding regimen selection, or by targeted toxicity prophylaxis, certainly should provide overall cost savings. For example, if an effective preventive agent were available for radiation-induced mucositis in patients with head and neck cancer, the projected savings could be calculated by deducting the cost of the intervention from the incremental cost (about $17,000) of mucositis.[48]

Not surprisingly, third-party payers have been reluctant to provide either coverage or reimbursement for genomic risk prediction, often still considering such tests to be investigational. Perhaps with broader test platforms— one test for multiple toxicities—and increasing validation of clinical utility, this stance will change. As the largest provider of health insurance in the United States, the government has established several initiatives to evaluate genomic tests and, in particular, to figure out ways to provide reimbursement. Although multiple U.S. agencies are involved in these efforts, those led by the National Human Genome Research Institute are noteworthy. From the patients' perspective, the value of genomic risk prediction seems recognized as patients have expressed a willingness to pay for information that better guides their treatment.

CONCLUSION

The application of genomics to cancer supportive care holds multiple opportunities to improve our understanding of the biology of regimen-related toxicities, to develop effective interventions, and, most importantly, to guide treatment decisions. A critical challenge to clinical implementation of this data will be ensuring that providers and patients understand what the data mean and how they can be used. Organizing and presenting data in such a way that results are actionable will be key. Provider education has been identified as a priority as genomics moves from the laboratory to the clinic.

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Clinical Research in Metastatic Prostate Cancer: A Focus on Impact and Value

Maha Hussain, MD, FACP, FASCO, and Robert S. DiPaola, MD

Despite substantial and continued reduction in mortality, prostate cancer continues to be a major cause of cancer death in men in the United States, with an estimated 27,540 deaths in 2015.[1] Historically, prostate cancer was one of the earliest examples of success in targeted therapy. More than 7 decades ago the key biologic and therapeutic breakthrough by Huggins et al established that prostate cancer is an androgen receptor (AR) pathway–driven and androgen-dependent disease, and that surgical or medical castration can induce substantial and prolonged regressions for patients with prostate cancer.[2,3] Despite a high response rate with androgen deprivation, most patients with metastatic disease progress to castration resistance, with a median survival in the prostate-specific antigen (PSA) era of about 4 years.[4]

In cancer therapy development, cytotoxic chemotherapy was one of the major products of the "war on cancer" during the past 4 decades. With androgen deprivation therapy (ADT) as a backbone of treatment for metastatic prostate cancer, efforts were directed at adding cytotoxic agents following castration resistance. Several chemotherapeutic agents were tested without a major breakthrough until 2004, with the approval of docetaxel, the first nonhormone agent that demonstrated a survival benefit in patients with metastatic castration-resistant prostate cancer (mCRPC), thus establishing a new benchmark and validating the role of targeting the microtubule in this disease.[5,6] Subsequent investments in prostate cancer research over the last 2 decades have led to major biologic discoveries with many targets and agents, resulting in several U.S. Food and Drug Administration (FDA) approvals (Table 1)[7] and additional testing in clinical trials.

ANDROGEN RECEPTOR SIGNALING CONTINUES TO MATTER BUT IS NOT THE WHOLE STORY

Perhaps one of the most important biologic discoveries was the understanding that progression to castration resistance is partly an adaptive process. Furthermore, despite clear evidence to support AR-independent mechanisms, unlike prior dogmas, AR-dependent signaling continues to be relevant.[8] Biologic data on the importance of AR signaling was the basis for developing several agents targeting AR or relevant enzymatic pathways. The principle was validated by results from phase III trials with abiraterone and enzalutamide that demonstrated survival improvements in patients with mCRPC.[9,10] The biologic discoveries regarding progression to castration resistance led to studies of several other experimental agents targeting additional pathways.[8,11-13] Efforts to target the immune system and bone have led to survival improvement with sipuleucel-T and radium 223 dichloride.[7] Therefore, in 2015, oncologists have several standard treatment options with proven clinical benefits to offer patients, both docetaxel-naive (sipuleucel-T, abiraterone/prednisone, radium 223 dichloride, enzalutamide) and docetaxel-treated patients (cabazitaxel/prednisone, abiraterone, enzalutamide, radium 223 dichloride), as well as an array of additional opportunities for clinical trials.

SO ARE WE THERE YET?

Over the past 2 decades, we have witnessed unprecedented progress in the understanding of the biology of prostate cancer and substantial returns on investment in research with the development of therapies for patients with mCRPC. This is reflected by multiple approvals that FDA has issued since 1996. These approvals were based on positive phase III trials for agents that have demonstrated an effect on overall survival, pain, or skeletal-related events—all clinical benefit outcomes relevant for managing this group of patients. However, in a similar time period, more phase III trials proved negative despite very promising biologic, preclinical, and phase II trial data (Table 2).[14-27] Surprisingly, multiple large studies that attempted to build on docetaxel by adding targeted therapy (DN101, GVAX, atrasentan, zibotenan, bev-

TABLE 1. U.S. Food and Drug Administration Approvals for Metastatic Castration-Resistant Prostate Cancer Since 1996

Category	Agent
Survival improvement since 2004	Docetaxel
	Sipuleucel-T
	Cabazitaxel
	Abiraterone*
	Enzalutamide*
	Radium 223 dichloride
Pain	Mitoxantrone
	Strontium
	Samarium
Skeletal-related events	Zoledronic acid
	Denusomab

*Pre- and post-docetaxel.

TABLE 2. Examples of Disproven Regimens in Phase III Trials

Category	Regimen
Miscellaneous targets	GVAX
	Docetaxel + GVAX
	Satraplatin
	Docetaxel + DN101
	TAK700
	Ipilimumab
Bone	Docetaxel + dasatinib
	Atrasentan
	Docetaxel + atrasentan
	Zibotenan
	Docetaxel + zibotenan
VEGF/Angiogenesis	Docetaxel + bevacizumab
	Docetaxel + aflibercept
	Docetaxel + lenalidomide
	Sunitinib

acizumab, dasatinib, aflibercept, and lenalidomide) were negative, which raises concerns about the adequacy and depth of current preclinical, diagnostic, and early clinical evaluation strategies and highlights the importance of the disease's biologic context.

Although these agents with demonstrated efficacy have been valuable to date, there is little question that current therapies have substantial limitations, including the fact that their effect on survival continues to be very modest (2 to 5 months' improvements).[7] Clearly, not all patients benefit. Furthermore, unlike many other solid tumors, we still use a one-size-fits-all treatment approach with no predictive biomarkers to maximize chance for benefit and reduce treatment burden on patients, both physical and monitory. Furthermore, although some trials were positive, these predominantly were conducted in an era in which essentially only one major treatment choice (docetaxel) existed. Also, many nonchemotherapy trials reported to date had a placebo control arm, which was a low bar to cross. Therefore, the true efficacy of current therapies in the current clinical context in which patients have undergone multiple prior treatments is unclear. In fact, several anecdotal and ob-

servational data are emerging on the suboptimal response to sequential AR pathway targeting with current agents.[28] The latter is an area that must be addressed considering all the implications.

THERAPY COST IS ESCALATING

"Price is what you pay. Value is what you get," is one of Warren Buffett's favorite admonitions, highlighting that price and value are not always the same. Perceived expectations, quality, value, effectiveness, and side effects are critical factors in a patient's satisfaction with his or her treatment. Historically, physicians, professional societies, and regulatory bodies in the United States have shied away from discussing financial costs of care. However, this discussion is very timely and critical. We owe it to our patients and society that therapy development must take into account the cost relative to the true benefit, value, and effect of the specific therapy. Table 3 highlights the average wholesale price of current agents. Although this may vary somewhat by vendor, or actual charge, the overall financial effect in the context of partial clinical activity calls for much needed improvement and reform of our current processes surrounding clinical trials and drug approval. The recent data on the detection of AR-V7 in circulating tumor cells from patients with castration-resistant prostate cancer and its association with resistance to enzalutamide and abiraterone,[29] if validated, is an example of the potential for better individualized selection of therapy to maximize benefit and reduce cost.

THE CHARGE MOVING FORWARD: A FOCUS ON TRUE IMPACT AND VALUE

Albert Einstein said, "Most of the fundamental ideas of science are essentially simple, and may, as a rule, be expressed in

> **KEY POINTS**
>
> - Several therapies targeting the androgen receptor and other pathways have improved survival and quality of life for patients with metastatic prostate cancer.
> - Many costly therapeutic clinical trial efforts have failed to improve outcomes.
> - Prostate cancer is a complex disease. Its biologic heterogeneity warrants that future clinical trials be carefully designed to achieve higher levels of clinical impact by attention to targeting more critical pathways; integrating improved diagnostics; well-designed and powered clinical trials using multi-targeted strategies; and optimized timing of therapy.

Table 3. Treatment Costs for Approved Agents[38]

Drug	Dose/Route	AWP Cost per Cycle (Drug Only)	Number of Cycles	Survival
Docetaxel	150 mg IV (75 mg/m^2 × 2 m^2)	$1,583.00	Median: 6	Yes
Cabazitaxel	50 mg IV (25 mg/m^2 × 2 m^2)	$10,797.68	Median: 6	Yes
Abiraterone	1,000 mg PO (30-d)	$8,852.02	Median: 8 ms	Yes
Enzalutamide	160 mg PO (30-d)	$10,026.04	Median: 8 ms	Yes
Sipuleucel-T	IV	$44,162.40	3 cycles	Yes
Radium 223 dichloride	IV	$22,126.80	6 cycles	Yes
Denusomab	120 mg SC	$2,115.72	Monthly	No
Zoledronic acid	4 mg IV	$838.29	Monthly	No

Abbreviations: AWP, average wholesale price; IV, intravenously; PO, orally; ms, months; SC, subcutaneously.

a language comprehensible to everyone." As a simple fundamental rule, therefore, our next efforts in clinical research must maximize clinical value and effect on patients, perhaps by simply using new technology to identify, critically evaluate, and target multiple critical pathways/targets simultaneously (or sequentially).

In the last 2 decades, the course of metastatic prostate cancer has evolved with improved management of age-associated comorbidities, PSA-driven stage migration, improved imaging, and the expansion of novel therapies. Therefore, the focus of therapy also must evolve and, much like other cancers, a cure should be the overarching objective. Short of a cure, there is a clear need for greater sustained therapeutic benefit. The latter necessitates substantially more investment in high-quality research and a critical review of our drug approval standards in this country, which currently do not incorporate major impact and value or cost of therapy relative to benefit. The latter, coupled with the cost of conducting clinical trials, does not necessarily encourage multitargeted combination therapy strategies; comparative effectiveness trials, with obvious clinical questions such as a comparison of competitor drug (e.g., abiraterone vs. enzalutamide efficacy in the same disease setting); nor moving therapeutics into earlier stages of the disease in which the therapeutic benefit is likely to be much greater.

The optimal development of studies with a higher effect must consider targeting multiple critical targets; utilization of improved technology, such as next generation sequencing; and new preclinical models with the potential to develop drug combinations and predictive biomarkers with analytic validity and greater clinical utility. Although the chromosomal translocation of *BCR* and *ABL* in chronic myeloid leukemia has served as an effective biomarker for a molecularly targeted therapy, it has become apparent that most other cancers have multiple driver alterations and adaptations thus requiring combinations of therapies for greater effectiveness. As additional potential driver mutations are now identified in prostate cancer through enhanced diagnostic technologies, such as next generation sequencing, we have new opportunities to design multitargeted approaches, perhaps aided by preclinical models to select best therapeutic combinations for clinical trials.[30-32] New models include the development of patient-derived tumor xenograft (PDX) models that allow testing of targeted agents, resistance mechanisms, and combinations in the preclinical setting in parallel with clinical trials in patients.[33] Recently, organoids have been created from patients with prostate cancer, allowing the potential for a novel preclinical model to test combination therapy.[34-36]

Taken together, an overall paradigm to create higher effect for value should include attention to (1) strong science that identifies critical targets and combinations in preclinical models; (2) optimization of combinations to target multiple critical pathways preclinically and clinically, with more precise selection of patients most likely to benefit using improved diagnostics; and (3) consideration to timing of therapy, with a rationale that therapy in earlier stages of disease may have more effect on outcome. A possible clue to the potential success of using both a multitargeted strategy and earlier introduction of therapy may be exemplified by the recently reported National Cooperative Group study, which study demonstrated improved survival by the concomitant use of docetaxel chemotherapy and ADT as compared to ADT only in patients with newly diagnosed metastatic prostate cancer.[38] The magnitude of survival improvement with early combination therapy (all patients, 57.6 vs. 44 months; high-volume disease patients, 49.2 vs. 32.2 months, as initially reported at the American Society of Clinical Oncology Plenary Session, 2014) represents multiples of those observed with current approved therapies in mCRPC.

CONCLUSION

The landscape of therapy and biologic understanding of metastatic prostate cancer is infinitely better compared to a decade ago, and it continues to evolve exponentially. However, the long list of negative trials clearly underscores the need that therapy development must focus on the totality of disease biology, including comprehensive molecular understanding of disease states; thorough validation of candidate targets/pathways/biomarkers of response and resistance; and multitargeted approaches to maximize therapeutic effects.

As oncologists, we owe it to our patients to raise the bar for future trials by requiring greater therapeutic efficacy; mini-

mizing use of placebo; avoiding artificial disease contexts such as pre- and post-docetaxel setting; avoiding artificial clinical benefit endpoints such as time to chemotherapy; developing multitargeted treatment strategies; and evaluating and maximizing cost-effectiveness. The latter strategies are not unique to prostate cancer. However, prostate cancer is a disease in which patient survival is measured in years, and although it continues to improve, it can become the model to begin to tackle and control the escalating costs of therapy while maximizing benefit. With smarter research and a higher bar for clinical trial expectations, we can raise the standards so that the return on investment for patients has more of an impact when patients are weighing their treatment options.

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The Future of Molecular Medicine: Biomarkers, BATTLEs, and Big Data

Edward S. Kim, MD, FACP

When I first entered the field of lung cancer, the seminal study published in the *New England Journal of Medicine* was a four-arm chemotherapy doublet study that showed no difference in effectiveness. Conclusions: All the drugs are the same, so use what you like for patients with advanced non–small cell lung cancer (NSCLC).[1]

Times have changed, and personalized medicine has become a reality. The era of "molecular medicine" has truly blossomed. Over the last decade, approximately 40 drug approvals were based on specific tumor biomarkers.[2] Options for patients have changed dramatically, from cytotoxic chemotherapy to molecularly targeted therapy. This concept has been standard for almost 2 decades for those treating patients with breast cancer (targeting HER2 and/or hormone receptors), but now patients with melanoma and lung cancer are included in this discussion. It is astounding how far treatments for each of these tumor types have progressed in the past 10 years. Melanoma treatment consisted of chemotherapy or interleukin-2 and now consists of RAF inhibitors and targeted immunotherapy, both of which have improved patient outcomes substantially: response rates and progression-free survivals have more than doubled. In fact, the progression-free survivals for molecularly targeted therapies exceed the overall survival numbers reported for chemotherapies. Lung cancer treatment has evolved from administration of chemotherapy yielding poor outcomes to biomarker assessments such as *EGFR, ALK,* and *ROS1.* Treatment with *EGFR* inhibitors (gefitinib, erlotinib, afatinib)[3-5] and *ALK*-based therapies (crizotinib, ceritinib)[6,7] have dramatically improved efficacy and quality-of-life outcomes. The notion that a patient with advanced lung cancer could be treated on oral biologic therapy for over 2 years without undergoing intravenous chemotherapy is astounding. For example, a patient with an *EGFR* mutation present in their tumor is treated with an *EGFR* tyrosine kinase inhibitor (TKI). Then the patient develops a *T790* mutation in the tumor and is treated with a *T790* TKI.[8]

As our desire for continued discoveries in tumor genetics increases, more and more data are generated and captured. Larger organized trials that prospectively capture biomarker and treatment data have emerged, and data analysis of these trials has become more complex. Adaptive trial designs, such as umbrella and basket trials, have become commonplace across academic cancer institutes and are emerging at community-based cancer institutes. As biopsies to obtain adequate amounts of testing for molecular studies are now the norm, repeat biopsies are now part of the armamentarium of procedures to best assess the tumor in real time following treatment. With electronic data capture processes (including electronic health records [EHRs] and national databases) also evolving, medicine is now faced with the concept of "Big Data": how to collect it, maintain it, integrate EHR big data with genomic big data, and thus, utilize it.

BIOMARKERS

The principle of identifying biomarkers to help guide patient treatment has been a longstanding research initiative. Early biomarkers and panels were largely classified as prognostic or predictive. They were not associated with a specific biologic therapy but rather defined the tumor characteristics, including response to therapy. Examples include Ki-67, carcinoembryonic antigen (CEA), and prostate-specific antigen (PSA). Breast cancer markers, such as hormone receptor status and HER2, were some of the earliest markers related directly to therapy. In lung cancer, validated markers associated with therapy began with elucidating that *EGFR* mutations were more prevalent in patients with adenocarcinoma, Asian ethnicity, and nonsmoking status and were correlated with high activity of *EGFR* TKIs (gefitinib, erlotinib, afatinib). However, more information was desired by researchers and treating physicians, and, more importantly, correlation with specific treatments was sought. Tumor registries were created to collect tissue and test utilizing evolving molecular

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panels. Such strategies have been developed across academic institutions, private enterprises, and government. Numerous cancer consortiums were developed in the 2000s that required submission of patient tissue along with clinical data.

The Lung Cancer Mutation Consortium (LCMC) is one of these efforts (www.golcmc.com). The LCMC, an initiative of the National Cancer Institute (NCI), comprises 16 leading cancer centers across the country, with the goal of providing clinicians with information on the types and frequency of mutations. Once identified, the mutations are matched with associated treatments and/or clinical trials, giving physicians more options to better care for patients with advanced NSCLC. Testing these mutations with various treatments could lead to identification of actionable mutations (tumors with a mutation that responds to specific treatments), which would expedite potential drug development. Over 1,000 patients (stage IIIB/IV, performance status 0 to 2) have been enrolled in the LCMC. The group has detected an actionable mutation in 64% of tumors from prospectively studied patients with lung adenocarcinoma.[9]

DIRECTOR'S CHALLENGE CONSORTIUM

The Director's Challenge Lung Study comprises gene expression profiles acquired on Affymetrix microarray chips from more than 400 specimens of early-stage lung cancer, with associated clinical and pathologic annotation available to the public for analysis.[10] The investigators reported a large, training-testing, multisite, blinded validation study to characterize the performance of several prognostic models based on gene expression for 442 lung adenocarcinomas. The hypotheses proposed examined whether microarray measurements of gene expression, either alone or combined with basic clinical covariates (stage, age, sex), could be used to predict overall survival in lung cancer subjects. Several models examined produced risk scores that substantially correlated with actual subject outcome. Most methods performed better with clinical data, supporting the combined use of clinical and molecular information when building prognostic models for early-stage lung cancer.[10] This has not yet translated into clinical practice, but highlighted that clinical information is still very important. This study also provides the largest available set of microarray data with extensive pathologic and clinical annotation for lung adenocarcinomas.

GENOME-WIDE ASSOCIATION STUDIES

Early efforts to collect large amounts of comprehensive data included genome-wide association studies (GWA study, or GWAS), also known as whole genome association study (WGA study, or WGAS). These studies involve rapidly scanning markers across the complete sets of DNA, or genomes, of many people to find genetic variations associated with a particular disease. The magnitude of data involved with GWAS requires thousands to tens of thousands of markers, compared to genomics that could require few to hundreds.

Other limitations of GWAS include the potential for high false-positive rates, which next-generation sequencing (NGS) may be able to overcome, and perhaps at a more economical scale. However, this is debatable until sufficiently larger data sets can be analyzed.

This method searches the genome for small variations, called single nucleotide polymorphisms (SNPs), which occur more frequently in people with a particular disease than in people without the disease. Information generated from these analyses can pinpoint genes that may contribute to a person's risk of developing a certain disease—including cardiovascular, pulmonary, or neurologic ailments, or cancer—or even determine an individual's sensitivity to drug metabolism. The National Institutes of Health (NIH) has developed a Database of Genotypes and Phenotypes (dbGaP; www.ncbi.nlm.nih.gov/gap) to archive and distribute the results of studies that have investigated the interaction of genotype and phenotype.

UMBRELLA TRIALS

Identifying a patient population that has the best chance for improved outcomes with therapy allows better assessment of safety and risk. Realizing phenotypic characteristics are limited in nature, clinical trials have focused more than ever on acquiring blood, tissue, and other biospecimens to identify biomarkers of response. However, the idea of finding the appropriate molecular phenotype/genotype of a patient and matching it with a molecularly tailored drug that will in turn lead to an overall survival advantage is still in the research and testing stage for the majority of patients with cancer. Clinicians have patients in whom impressive results have occurred on a mostly case-by-case basis. The best drugs or combinations of drugs for individual patients are still speculative.

BATTLE

My colleagues and I initiated the BATTLE trial (Biomarker-Based Approaches of Targeted Therapy for Lung Cancer Elimination) in 2005. In the study, patients with previously diagnosed and treated lung cancer underwent a new real-time biopsy to assess biomarkers. These biomarkers were utilized in an adaptive manner to select treatment recommendations with one of several biologic agents. BATTLE was conducted before any drugs were approved with companion diagnostic biomarkers. The trial provided an important proof of principle that repeat biopsies could be performed safely and expeditiously in patients who were previously treated for lung cancer.[11] Subsequent BATTLE trials have been initiated based on our initial trial.

I-SPY 1 and I-SPY 2

Other trials have utilized similar concepts across a variety of disease types (Table 1). The I-SPY breast cancer studies were sponsored by a combination of public and private organizations, including the Foundation for the National Institutes of Health, NCI, U.S. Food and Drug Administration (FDA),

TABLE 1. Selected Umbrella and Master Trials

Title	Short Name	Sponsor	Accrual Dates	Estimated Enrollment	Cancer Types	Treatment	Biomarkers
Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination	BATTLE	MD Anderson Cancer Center	2006-2015	250	Non-small cell lung	Erlotinib, sorafenib, vandetanib, erlotinib + bexarotene	EGFR, KRAS, BRAF, CCND1, VEGF, VEGFR-2, RXRs, cyclin D-1
BATTLE-2 Program: A Biomarker-Integrated Targeted Therapy Study	BATTLE-2	MD Anderson Cancer Center	2011-2017	450	Non-small cell lung	Erlotinib, AZD6244, MK-2206, sorafenib	EGFR, KRAS, EML4/ALK
Lung Cancer Master Protocol	Lung-MAP	Southwest Oncology Group	2014-2022	Up to 10,000 screened	Squamous cell lung	MEDI4736, GDC-0032, palbociclib isethionate, AZD4547, rilotumumab, docetaxel, erlotinib hydrochloride	PIK3CA, CCND1, D2, CDK4, FGFR
Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And Molecular Analysis 1	I-SPY1	National Cancer Institute	2002-2010	356	Stage II-III breast	Standard neoadjuvant anthracycline-based chemotherapy, with or without a taxane	Hormone and HER2 expression
Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And Molecular Analysis 2	I-SPY2	QuantumLeap Healthcare Collaborative	2010-2015	800	Locally advanced breast	Standard therapy, AMG 386, AMG 479 (ganitumab) + metformin, MK-2206 with or without trastuzumab, AMG 386 + trastuzumab, T-DM1 + pertuzumab, pertuzumab + trastuzumab, ganetespib	Hormone and HER2 expression
Molecular Analysis for Therapy Choice	NCI MATCH	National Cancer Institute	Opening early 2015	Up to 3,000 screened for biomarkers, approximately 1,000 treated	Advanced solid tumors, lymphoma	20-25 targeted agents (e.g., imatinib, erlotinib, crizotinib, trastuzumab, vemurafenib)	EGFR, HER2, MET, BRAF, NF1, GNAQ, GNA11, TSC1/2, PTEN, Patch, NF2, ALK, ROS, FGFR
Initiative for Molecular Profiling in Advanced Cancer Therapy (IMPACT) Trial, An Umbrella Protocol	IMPACT	MD Anderson Cancer Center	2009-2016	Approximately 5,000	Advanced cancers	None	EGFR, VEGF, HIF-1α, PI3K, RAS, RAF, MEK, cytokines, interleukins
Molecular Profiling-Based Assignment of Cancer Therapeutics	NCI MPACT	National Cancer Institute	2014-2017	700 to be screened, 180 to be enrolled on treatment	Advanced cancers	Temozolomide, everolimus, carboplatin, trametinib DMSO, ABT-888, MK-1775	DNA repair pathways, PI3K, or RAS/RAF/MEK
Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial	ALCHEMIST	National Cancer Institute	2014-2020	Up to 8,000 screened	Early-stage non-small cell lung	Erlotinib hydrochloride, crizotinib	EGFR, ALK

Safeway Foundation, Biomarkers Consortium, Quintiles, and QuantumLeap Health Care Collaborative. The goal of I-SPY 1 was to identify predictors of response to neoadjuvant chemotherapy for women with stage II/III cancer. A total of 356 women were enrolled; biomarker information and MRI results were obtained. Researchers found that certain tumor profiles responded better than others to particular drugs. Results from I-SPY 1 guided the design of I-SPY 2, an adaptive, randomized trial that uses early data to guide treatment decisions for those enrolled later in the trial. Approximately 800 women will be enrolled in this trial of multiple drugs.[12]

ALCHEMIST

The NCI has launched initiatives to study patients with unique biomarkers and targeted therapy in both early- and advanced-stage cancer settings. The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST) series is focused on patients diagnosed with early-stage lung cancer. The series of trials consists of a screening trial and two treatment trials (*EGFR*-targeted therapies and *ALK*-targeted therapies). Approximately 6,000 to 8,000 patients will be enrolled in the screening trial over the next 5 to 6 years with the goal of determining if selection of therapy based on these molecular markers leads to improved survival. Tumor biopsies from these patients will be evaluated for *EGFR* and *ALK* abnormalities. Patients whose tumors harbor one of these mutations will be directed into the appropriate biologic treatment trial (erlotinib if *EGFR* is mutated and crizotinib if *ALK* is abnormal vs. placebo). Each treatment trial is expected to enroll approximately 400 patients.[13]

MASTER STUDIES
NCI MATCH

Another NCI-sponsored study, NCI MATCH (The NCI Molecular Analysis for Therapy Choice Trial), will enroll patients with advanced solid tumors (gastrointestinal stromal tumor, NSCLC, breast, gastric, melanoma, thyroid) and lym-

phomas. Biopsies from approximately 3,000 patients will undergo testing for abnormalities that may respond to targeted drug therapies. Of these patients, up to 1,000 will then participate in phase II clinical trials of targeted drug therapies. The patients will be matched to the drug based solely on the genetic abnormality, not on the type of cancer. NCI MATCH is a master trial, meaning that new drugs can be added to the trial at any time. The primary endpoint for this trial is response, however, progression-free survival will also be assessed.[14]

A new public/private cooperative effort is Lung-MAP (Lung Master Protocol). This study will enroll 500 to 1,000 patients diagnosed with advanced, previously treated squamous cell lung cancer each year. The molecular profiling is done with a central commercial panel and places patients into different arms with biologic therapies. One feature of this study is that patients who do not meet the criteria for treatment with a targeted therapy are placed into a trial involving a nontargeted investigational treatment. The primary objective of this trial is to determine if the efficacy of targeted therapy is better than that of standard therapy.[15]

M-PACT

In the NCI-sponsored M-PACT (Molecular Profiling–Based Assignment of Cancer Therapeutics trial), patients with advanced tumors that have progressed on at least one line of standard therapy undergo tumor biopsy to determine if a mutation is present. Those who do not have an identifiable mutation are removed from the trial. Those who do have a mutation are randomly assigned to receive either treatment with a drug known to target their mutation or treatment with a drug not known to target their mutation. Cross-over is allowed for those who experience disease progression after receiving treatment with a drug not known to target their mutation. Tumor response and 4-month progression-free survival are the endpoints in this trial. Accrual to this trial began in 2014 and approximately 700 patients are expected to be screened, with over 150 to be enrolled in a treatment arm. The goal is to determine whether therapies targeting a mutation can work in the metastatic setting.[16]

There is a need to test the approach in different settings, leading to many umbrella and master studies required to answer the overarching question of whether therapies targeting molecular aberrations lead to better outcomes for patients over standard chemotherapy, and in what types of patients, tumors, or aberrations these treatments work (or do not work). The importance of these efforts is not only the testing of the specific targeted therapies, but the collection and storage of centralized tissue and molecular data. These collections will allow large amounts of data to be analyzed with the hope of someday developing predictive treatment models for patients.

BIG DATA

Big data is defined as any voluminous amount of structured, semi-structured, and unstructured data that has the potential to be mined for information. More specifically, big data is any

data whose scale, diversity, and complexity require new architecture, techniques, algorithms, and analytics to manage it as well as to extract value and hidden knowledge from it. Big data expands across four fronts: velocity, variety, volume, and veracity (Table 2).[17,18]

Capturing big data in databases may help formulate hypotheses for testing. Statistical testing can be performed on pre-existing data to facilitate this process. However, big data collection can be compromised by bias in medical records, lack of data validity and reliability, and technology challenges. The potential for misinterpretation of the data is paramount. Additionally, the structure of electronic medical records may be poorly suited for adequate data abstraction and are certainly not suited for numerous secondary analyses. Many institutions also have different platforms, which can impede data integration. Attention to privacy, sharing, transparency, and stewardship are all guiding principles for big data collection and analysis.

Medicine, specifically cancer medicine, is encountering this dilemma. As the amount of information exponentially increases (patient clinical information, pathology, biomarkers, treatment outcomes, and patient questionnaires), the prospect of harnessing and processing this data is daunting. However, the potential rewards make it worth the effort. Numerous companies and researchers are working to integrate and interrogate these data sets with expectations that they will identify new opportunities for treatment, diagnosis, prognosis, and prevention. Nontraditional groups are joining the foray into this area, including Google and financial institutions, because of their ability to collect a variety of data on inordinately large numbers of individuals and variables (e.g., search, purchasing, and other behaviors).

ASCO CANCERLINQ

The American Society of Clinical Oncology (ASCO) has established an important initiative called CancerLinQ™ (www.CancerLinQ.org), a health information technology

TABLE 2. The Four Fronts of Big Data

Fronts	Description
Velocity	The velocity of cancer medicine is ever increasing as the number of patient encounters, molecular tests, and treatments grows.
Variety	Data platforms in cancer medicine continue to rapidly evolve. The electronic health record is becoming a better resource as a database. More and more hospital systems are incorporating telemedicine which enlist mobile connectivity. Archived data mining is now becoming active data searches.
Volume	The amount of information that is being generated by cancer medicine is being measured in the scope of peta- and exabytes. Storage solutions must be forward-thinking, including current cloud sourcing.
Veracity	The reliability of data sources in the health care setting is not always ideal, as most systems are not set up for research. Large data sets can be subject to bias. We should be prepared to acknowledge the limitations of our data.

platform that plans to collect information from the experiences of patients with cancer. The goal of this big data collection will be to improve the quality and value of cancer care. Data will be collected from the electronic health records of patients across the United States and will be restructured and stored into one single database that will be able to provide clinical decision-making support for health care providers. The information from patients and providers will be continuously collected, thus enabling further refinement of the decision-making algorithm. ASCO has currently created a prototype platform and has initiated 15 practice sites to collect data from over 500,000 patient experiences.[19]

Big data projects like CancerLinQ include strategic, technical, and regulatory challenges, but ASCO has established a robust external advisory structure to guide its development. An example of clinical utility could be in immunotherapy treatment. As melanoma, renal cell, and lung cancer have immunotherapy as treatment options, harnessing numerous patient encounters and clinical data could create guidance for clinicians in managing not only the disease process, but also side effects from the treatment. This type of data would be valuable in helping predict responders and nonresponders, perhaps predict who will experience side effects, and more importantly, help keep patients on treatment longer, which may translate into better survival and quality of life.

PRECISION MEDICINE INITIATIVE

In his 2015 State of the Union Address, President Barack Obama proposed a new initiative aimed at increasing our capacity to research, and ultimately deliver, precision medicine across disease types. President Obama has designated over $215 million to support the collaborative efforts of the NIH, FDA, and Office of the National Coordinator for Health Information Technology on this Precision Medicine Initiative. With the initial focus on cancer, the President has proposed to create a research cohort (partially through the use of existing resources and partially through upwards of 1 million new accruals) in which patient tissues and clinical data will be collected, stored, and analyzed. This big data will be used to enhance our existing knowledge of molecular medicine and develop individualized, molecular approaches to cancer treatment. The President's new initiative is clearly at the intersection of biomarkers and big data.[20,21]

CONCLUSION

The era of personalized medicine continues at a rapid pace. The practice of medicine now requires not only a clinical examination, but also molecular testing, novel therapeutics, research trial awareness, and perhaps utilization of information obtained from big data in the near future. Integration of these tools will enable providers to deliver better, more comprehensive care. Much work still needs to be performed, and more tools needs to be developed and refined, to help providers and clinicians achieve the best results.

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Towards a Personalized Treatment of Head and Neck Cancer

Andrew M. Gross, CPhil, and Ezra E.W. Cohen, MD

There is increasing excitement surrounding the surge of data that has emerged throughout various sectors of oncology research, which often seems like hyperbole. Although the use of data to inform decision making is far from novel, the emergence of inexpensive and ubiquitous computing power and storage has bolstered our ability to produce data-driven insights and has ushered in the era of "big data." The essence of the big data paradigm is simple: given enough data, machines can generate insights equivalent to or sometimes even exceeding experts in the field. One example of the application of this paradigm lies in the field of natural language processing where the use of giant collections of text provide better results with much simpler models and less expert input.[1] In contrast, notable failures exist including the buildup and subsequent implosion of Google Flu Trends to predict the onset of the flu season.[2,3]

Alongside these developments, the field of cancer has seen a bolus of data emerging from a combination of old and new sources. The digitization of hospitals and the spread of electronic medical records have created large archives of traditional data, making meta-analyses of large patient cohorts almost facile. Furthermore, the adoption of high-throughput molecular profiling and the plummeting costs of genetic sequencing are creating new opportunities to probe the inner-workings of healthy and diseased cells. Although the idea of personalized medicine is clearly not new, our ability to accurately quantify the defining characteristics of an individual patient's tumor lends hope that a targeted attack against its specific biology is possible.

In head and neck squamous cell carcinoma (HNSCC), such molecular biology has proven pivotal to our understanding of the disease. Starting with targeted studies of mRNA, protein expression, and analysis of chromosomal gains and losses, the field slowly pieced together a model in which epidermal growth factor receptor (*EGFR*) expression is activated and chromosomal abnormalities accumulate, often alongside mutations to the *TP53* gene.[4-6] As cohorts became larger and more high-throughput analysis such as microarrays and sequencing technologies became available, it became clear that the picture was far more complex and that there exist different subtypes of the disease.

As data acquisition becomes readily available with the rise of high-throughput sequencing, our understanding of tumor biology is actually beginning to blur. Although more and more driver genes are being discovered, it is exceedingly clear that the molecular characteristics of no two tumors are identical and that the biology driving tumor initiation and progression may be far more complex than originally envisioned. As genomic profiling in cancer becomes ubiquitous, the promise of the big data paradigm may affect patients with HNSCC by enabling personalized monitoring, diagnosis, and treatment of this disease. Although the dystopian vision of machines treating patients is not likely to become a reality anytime soon, the ability to use systematic data to inform better patient treatment is all but inevitable.

MOLECULAR STRATIFICATION OF HEAD AND NECK CANCER

In the late 1990s, the convergence of epidemiological and molecular studies on the influence of HPV in cancers of the oropharynx led to the first molecular stratification of head and neck cancers. The ability within the research community to detect HPV DNA by sequencing-based methods allowed for comparison of HPV-positive and HPV-negative groups with other molecular measurements and clinically obtained variables. In parallel, analysis of increasingly large molecularly characterized cohorts has enabled a more refined understanding of the heterogeneity of this disease. The rise of such cohorts alongside the continued use of model systems has allowed for exquisite understanding of the key events that drive HNSCC and even how these events interact with each other. Whereas the molecular details of HPV-positive and HPV-negative HNSCC are fascinating, we refer the reader to a number of recent papers and reviews that comprehensively cover these facets of the biology of HNSCC tumors.[7-10]

The picture that eventually emerged was one of very different cancers, with HPV-positive patients being far less likely to have the traditional risk factors of smoking and drinking while having substantially better cure rates than their HPV-

negative counterparts.[11] Underlying these differences in clinical phenotypes are distinct molecular characteristics of HPV-positive and HPV-negative tumors.[12] Gene expression studies have pointed to subtypes of the disease with different clinical and molecular characteristics. A recent analysis based on four discovery cohorts and two independent validation datasets classified HNSCC into three super groups called inflamed/mesenchymal (IMS), basal (BA), and classical (CL) based on previously used nomenclature.[12] Interestingly, HPV-positive tumors fell into only two of these groups (IMS and CL), whereas the BA group consisted exclusively of HPV-negative cancers. Furthermore, the classification appears to be prognostic for overall survival even within the HPV-positive tumors where the IMS HPV-positive group, enriched for immune-related genes, had the best outcome.

TP53 mutations were shown to be exclusive to HPV-negative tumors, presumably as a result of the phenocopying effect of E6 viral protein-mediated TP53 degradation. Similarly, whereas CDKN2A has been shown to be affected by copy number losses or mutations to the coding sequences of the gene, this was not seen in HPV-positive tumors as a result of its inactivation by the E7 viral protein. Other notable differences are seen in kinases that could be potential targets for therapy including more frequent mutation of *PIK3CA* and *FGFR 2/3* in HPV-positive tumors contrasted with amplification of *EGFR, FGFR1,* and *CCDN1* seen exclusively in HPV-negative tumors.[12-13]

In tumors lacking HPV infection, long-term studies of *TP53* mutation have shown that its presence is associated with poor outcomes, an effect that seems to be accentuated by the functional effect of the mutation. Recent work by Gross et al looking across multiple data-layers has refined the interpretation of *TP53* mutations by showing that they usually co-occur with loss of the 3p chromosomal region and that the adverse prognostic effect coincides with the combinations of the two events.[14] The putative gene(s) on 3p have yet to be fully elucidated but one candidate is *FHIT*, which functions as a tumor suppressor and has been linked with radiosensitivity, perhaps explaining its key role in HNSCC.[15]

Larger cohorts such as The Cancer Genome Atlas (TCGA) have facilitated attention to increasingly rare genomic drivers of the disease. One example is Caspase 8 mutation, which only compromises approximately 8% of the TCGA patient cohort. Despite its relatively low frequency, this event has proven interesting as it occurs in mutual exclusion of the *TP53* mutation/3p deletion event, and has been shown to accelerate tumor growth through inhibition of death receptor mediated apoptosis pathways.[14,16] These tumors seem to have developed from a very different mechanism of oncogenesis than either their *TP53* mutated, or HPV-positive counterparts, and patients with the alteration would likely benefit from different treatment strategies.

Even as we begin to understand the drivers of HNSCC progression, new unsolved problems arise such as understanding the heterogeneity of the disease and the interplay of clonal populations within a single tumor. Current studies rely on molecular measurements taken from a single tumor sample at a single time-point, usually before intervention. The observation that patients with a high degree of intratumoral heterogeneity tend to have worse outcomes proposes new research directions to quantify the tumor not as a single unit but as a collection of diverse cellular populations.[17] Profiling at multiple sites within a tumor as well as multiple time-points along the treatment and progression of the tumor will add a new dimension to our understanding of HNSCC. However, to understand this more complex data, bigger and more phenotypically rich cohorts will be required.

THE RISE OF BIG DATA IN CANCER

In the age of the $1,000 genome, a new market for consumer genomics has emerged that promises both immediately actionable results to the patient as well as a treasure trove of data for the institutions overseeing its collection and maintenance. At its current state, clinical sequencing remains an optimistic enterprise with few truly actionable events detected by such assays. Although current prospects for such personalized

FIGURE 1. Schematic of the Precision Medicine Paradigm on the (A) Population and (B) Individual Patient Levels
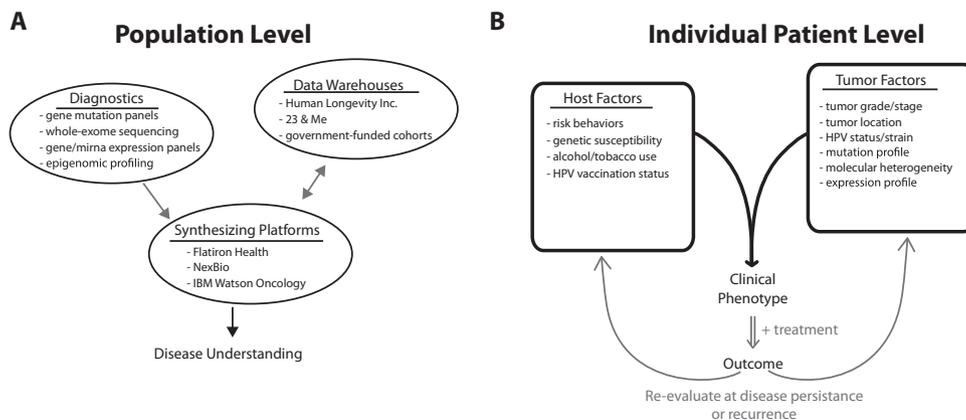
treatments are poor, such large numbers of patients will facilitate better development and deployment of the next generation of cancer drugs, and provide patients and their physicians with a much more precise diagnosis of their disease.

TEACHING AN OLD DRUG NEW TRICKS

With consortia such as TCGA and the International Cancer Genome Consortium leading the way, the utility of large collections of molecularly profiled patients has become very clear. The amount of data available translates into improved power to explore the increasingly large list of molecular events that play a role in tumor initiation and progression.[18] These discoveries in turn provide opportunities for promising leads for drug development and even enable repurposing of drugs traditionally used for other diseases. For example, metformin, a biguanide hypoglycemic drug used to treat diabetes, is being explored in multiple cancers including HNSCC because of its metabolic effects and ability to activate AMPK.[19] Those properties open the door to targeting a variety of cancers where analysis of multiomics data reveals relevant functional alterations.

Moreover, reanalysis of clinical trials with new information on patients' genetic backgrounds will potentially facilitate repurposing of old drugs for patients with specific tumor characteristics. Such analysis has already shown success in a study of extraordinary responders that analyzed patients with exceptional responses in otherwise failed clinical trials.[19] These patients' response to targeted drugs can often then be analytically attributed to molecular alterations within their tumor, providing new leads for prospective study of the drug in a specific molecular context. Although promising, the large number of potential biomarkers gleaned from such post hoc analyses makes over-testing a real possibility and generated hypotheses will still need to be subjected to prospective studies. To combat approval of indications resulting from spurious correlations, regulators will have to ensure strict adherence and definition of design protocols. Furthermore, new clinical trial designs that randomize with specific knowledge of patients' genomics will be needed to allow for approval of targeted drugs for targeted uses.

THE INCOMING DATA DELUGE AND WHY IT MATTERS

With direct and indirect sources of revenue becoming increasingly certain, numerous private entities have emerged alongside research institutions (Fig. 1). Diagnostics have emerged from new (Foundation Medicine) and established (Sequenom, Illumina) companies offering targeted sequencing panels searching for actionable mutations in patient tumors. Data warehouses (Human Longevity, Inc., 23 and Me) are now offering cheap sequencing in exchange for control of market share and patient data. Middle layers (Flatiron Health, NextBio) are beginning to emerge to link such information directly to physicians as well as research entities along the spectrum of the drug development pipeline. Alongside

these efforts, personalized and precision-medicine initiatives are being declared across the world, which promise to compile genomic and phenotypic data in public efforts to provide rich datasets to the research community.[21-23]

Although it is clear how massive databases of molecular tumor profiles will improve our understanding of the disease on a population level, more work is needed to understand a single patient's tumor well enough to offer truly personalized treatments (Fig. 1). Much as our current understanding of HNSCC facilitates broad divisions of the patient population by factors such as smoking status, HPV infection, expression subtypes, or *TP53* mutation, the increased availability of data will allow for finer dissection of the population. Data aggregators will enable anonymized access to tumor profiles and access to treatment courses and outcomes of patients with similar tumors. New methods will be required to determine the key aspects driving the similarity of two tumors, be they anatomic, genetic, and/or histologic. Standardization of reporting protocols and data exchange will create a larger pool of potential matches to a given patient and allow for more informed treatment decisions to be made. Regulatory protocols and data security measures will need to be implemented to ensure the privacy of all parties involved.[24]

SMARTER OUTCOMES

It remains unclear whether a tumor's molecular characteristics will remain static throughout treatment or alter throughout therapy. The relative accessibility of HNSCC tumors should allow for exquisite tracking of the characteristics of a patients tumor but has been underutilized thus far. Small studies have been able to demonstrate target inhibition or pharmacodynamic effects of a drug, but exploration of new models and protocols for adaptive treatment regimens has yet to be assessed.

The incorporation of targeted therapy will change how we approach initial therapy and assess drug resistance. Combinations of drugs may be developed to preemptively silence resistance pathways.[25] Although the use of single targeted drugs may attack a key feature or vulnerability of the tumor, it is likely that a more detailed understanding of a patient's tumor and the specific pathways being altered will be necessary for effective combinatorial targeting. Even if a patient is likely to develop resistance, if it is predictable and its manifestation has its own treatment strategy, multistage treatment plans with careful planning and monitoring may be in order. Making these alternative treatment paradigms a reality will require a wide range of advancements such as better tissue biopsies or noninvasive measurements of tumor DNA from blood to track the molecular makeup of the tumor, as well as faster experimental and analytic pipelines for ensure timely treatment.

Alongside genomic advancements, the digitization of medical records will also allow for rich recording of patient outcomes past the standard metrics of progression-free interval and overall survival. Alternative metrics such as patient heart rate, activity levels, and sleep quality will be measured by specialized and/or consumer sensors, bands, and watches. Such rich measurements will be aggregated and used to inform

treatment by allowing for unbiased understanding of the effects of a treatment on quality of life.[26]

THE FUTURE OF PERSONALIZED MEDICINE

Genomic data is flowing at unprecedented rates. The biology of HNSCC is being dissected in increasingly remarkable detail. Smarter drugs are in the pipeline to cater treatment to the specific genetic makeup of a patient's tumor. Private enterprise has embraced the genome era and begun construction of giant silos of patient data. Precision medicine has reached the mainstream and is being heralded as the next great step in

the "war on cancer." However, significant hurdles remain before big data can be translated into better outcomes for patients with cancer. Determining which elements of big data are biologically and clinically relevant will require the development of new analysis methods, changes in clinical trial design, new infrastructure for data sharing, and, perhaps most importantly, close collaboration between bioinformaticists, oncologists, and the pharmaceutical industry.

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Disclosures of Potential Conflicts of Interest

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Medical Education: Perils and Progress in Educating and Assessing a New Generation of Learners

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Tinsley Harrison is well recognized as one of the premier medical educators in history.[1] However, the social, political, and cultural forces that shaped the health care landscape have changed since Harrison's time. In the mid-20th century, teaching was an endpoint in and of itself. Patients were largely indigent, and health care financial pressures were different, allowing teacher and trainee to spend ample time discussing and dissecting individual patient cases. Bedside teaching was paramount, and the trainee's most valuable learning occurred in the hospital through real-time patient-based cases. Duty hour restrictions did not exist. Moreover, students were expected to adapt to the methods of the teacher, a one-size-fits-all policy.[2]

In the late 20th century, the financial landscape of medicine changed, and with this change an altered view of medical education evolved.[2] Managed care had substantial effects on health care delivery and created new financial pressures for academic institutions now emphasizing patient volumes and rapid turnover to capture clinical revenues. Unfortunately, medical education, which required substantial amounts of faculty time and resources, took a back seat. Educators noted substantial pressure to increase volume and efficiency, eroding time for educational activities. Although the social contract of the Harrison-era emphasized patient care, the new social contract in the managed-care era emphasized cost containment and efficiency.[2] This ran counter to traditional medical education that emphasized the slow, methodical development of compassionate and intellectually thoughtful providers who could learn in a medical "utopia" regardless of cost to the patient or institution.[3] These new financial pressures served to drain key resources for medical education and further eroded the learning environment. Faculty development in medical education also suffered. Why develop a medical educator when medical education does not pay and, in fact, slows down potentially profitable providers?[3,4]

The 21st century has continued to emphasize fiscal responsibility in medicine with attendant pressures on academic institutions. Although these issues once stalled medical education, the new social contract demands medical cost containment and an emphasis on personalized care. This has created new opportunities for the medical educator. The public now demands caring, competent physicians who participate in quality and performance improvement activities as well as medical training that is mindful of global medical fiscal responsibility.[2] In fact, one could argue that the present day social contract, a melding of Harrison-era and managed-care era, forces to produce a new physician phenotype. Most importantly, medical educators will play a key role in the development of this knowledgeable, compassionate, and fiscally responsible provider. Thus, professional development of the medical educator in the 21st century is critical and represents "the personal and professional development of teachers, clinicians, researchers, and administrators to meet the goals, vision and mission of the institution in terms of its social and moral responsibility to the communities it serves."[5]

WHAT IS PROFESSIONAL DEVELOPMENT? WHY IT IS IMPORTANT?

Professional development is a planned program to encourage individuals and institutions to improve practice and manage change, which in turn can lead to improvements in learning outcomes for students and physicians and, ultimately, improved patient and community outcomes.[5,6] Professional development includes any individual involved in undergraduate or postgraduate medical education[5] and aims to promote the establishment of communities within academic institutions that value teaching, learning, leadership, and research in medical education.[5,7] A successful professional development program can be central to the growth and prosperity of an academic institution, but can also attend to the growth of the individual. This promotes a culture that values both institutional and personal growth.[5] McLean et al have suggested that an institution that values both the professional and personal development of its staff will nurture faculty members who are interested in becoming educa-

tional scholars, leaders, researchers, and/or service providers.[5] The establishment of a successful faculty development program can facilitate educational change and improvements in the academic medical environment.[8] Within the United States and abroad, many institutions established professional development programs decades ago to improve their educational missions with demonstrated success.[6-19] Nationally, professional organizations such as the Accreditation Council for Graduate Medical Education (ACGME) have modified how we evaluate and promote trainees to best support the evolving societal expectations of the modern physician.[20] Thus, change has brought new opportunity to medical education and laid the foundation for a utopia of sorts within this arena. Although this seems like a tall order, this goal can be achieved through innovative medical education programing, and we now enter a renaissance period in medical education to support this end product. We are already seeing the early influence of this new movement on both a national and an institutional level.[5,21,22] Educators have a responsibility to train the present and next generation to carry the torch, not only to service a new generation of learners, but also to create an innovative army of educators to maintain and, ultimately, build on the momentum of educator creativity and productivity.

Let's return to the original question, what would Tinsley Harrison do? In his book, *Tinsley Harrison, MD: Teacher of Medicine*, James Pittman notes: "He (Harrison) died a bitter critic of the mindless overuse of the medical technology he himself had helped develop and of what he considered the disoriented nature of universities and their even more disoriented medical schools."[1] Although Harrison might have been skeptical about some aspects of the modern health care landscape, one would suspect he would stand behind a movement that upholds medical education as a platform to enact monumental change in health care delivery with the ultimate goal of optimizing patient care.

PRINCIPLES OF LEADERSHIP EDUCATION AND DEVELOPMENT FOR MEDICAL EDUCATORS

George E. Thibault of Harvard Medical School noted, "curricula were developed first, and then students were taught and assessed. Now, curricula should be designed last, after public health needs are assessed, and they should include innovations such as interprofessional and interdisciplinary training, new models of clinical education, new content to complement the biologic sciences, competency-based and individualized education tracks to speed the training process, and incorporation of new educational technologies."[23] A changing health care landscape supports reform in medical education. To meet the learner "right where they are" regarding today's health care system needs, teachers must modify how they teach.

New challenges within health care systems and population health imply a need for faculty development of the medical educator to meet these new challenges. Additionally, professional organizations such as the ACGME have adopted new accreditation and evaluation systems to ensure graduating physicians can support and promote the new demands of our nation's health care needs. Specifically, physicians are no longer expected to function as independent actors but to function as leaders and participants in team-oriented care.[4,20] Patients, payers, and the public demand their providers are technologically adept, practice proactive evidence-based medicine with cost containment, include the patient in their decisions, and utilize health information technology to improve care for individuals and populations.[4,20] To meet these demands, the ACGME has produced the Next Accreditation System (NAS), which educators now need to develop mastery over and to develop novel programming to support others.

Developing such programs is not without potential challenges, but the potential rewards remain substantial on a personal, institutional, and national medical landscape perspective.[24] Table 1 demonstrates potential challenges and wins in terms of medical educator development and community outcomes. In truth, the challenge becomes not how we can afford to invest in such programming but rather how can we afford not to? Educational standards cannot afford to lag behind delivery-system change. Investments in innovative programming and development of the new medical educator are required to meet this challenge.

THE EVOLUTION OF TEACHING AND ASSESSMENT STRATEGIES

External forces affecting change in medical education include the social contract that requires a better assessment method to judge the competence of physicians before entering practice in the modern health care environment. The ACGME has developed the NAS to begin to meet this need. The NAS now requires all medical training programs to use competency-based milestone assessments. Previously, trainees were evaluated on broader core competencies that included patient care, medical knowledge, interpersonal and communication skills, professionalism, practice-based learning, and improvement and systems-based practice.[25] Faculty did not always receive training and may not have understood these terms; making honest, concrete evaluations of observable trainee progress and competence difficult, often resulting in inflation of skills and knowledge levels. In contrast, the NAS focuses on outcomes-based milestones for trainee performance within these aforementioned six domains of clinical competence. An example of such a milestone that fulfills the new social contract is: "Responds to each patient's unique characteristics and needs." The clinical competencies that this milestone speaks to are professionalism and interpersonal communication skills. Although this might seem like another esoteric description, the milestone itself is broken down into key observable behaviors "as determined by individual programs." For example, observable behaviors that may inform this milestone include: the trainee discussing end-of-life issues with a patient of a different cul-

TABLE 1. Potential Outcomes of a Successful Medical Education Program

Outputs	Activities to Support Outputs	Resources Required for Outputs	Potential Outcomes Related to Successful Outputs
Educationally sound curriculum or curricular intervention to meet the needs of changing health care landscape	Curricular development training including project-based experiential learning in curriculum development and implementation, and skills development in curricular evaluation	Faculty experts in curricular development Funding to support program Faculty time	Compassionate and knowledgeable providers who deliver efficient and cost effective care
Scholarship in medical education	Training in research design and methodology, data analysis, manuscript writing, grant writing, and statistics	Funding for research Faculty trained in medical education research methodology Possible medical education cooperative groups Faculty time	Innovative educational practices Dissemination of new knowledge
Leaders trained specifically to address, effectively navigate, and develop programing in an increasingly complex medical education and health care landscape	Training in leadership skills development, maintaining and developing organizational efficiency, development of personal leadership style, and how to develop people	Mentorship Faculty time Networking community Educators in leadership development Funding	Changes in organizational contexts and leadership roles Institutional and professional society support and promotion of faculty as medical educator

tural/ethnic background, trainee discussing informed consent with a patient with low literacy level, etc. The trainee is then judged based on an entrustment scale that describes the level of trust that the trainee can carry out the given activity competently and independently. For example, the trainee can perform the skill with distant supervision, the trainee can perform the skill with direct supervision, the trainee is aspirational and can teach this skill to others. This gives the faculty a more grounded view of how to evaluate trainees to ascertain clinical competence in an area of emphasis in modern-day medicine/health care. However, activities need to be prescribed that allow observable behaviors to ensue. Trainees will be evaluated on a trajectory of competence and should demonstrate progress, not perfection, as they advance toward independent practice. However, the question remains how is the behavior measured or observed to accurately place the trainee on a milestone trajectory? Additionally, what activities meet the millennial learner "right where they are" and, thus, provide a meaningful educational experience? To meet these challenges, educators need to cultivate and employ new assessment strategies. Some of these new processes are described below and placed in context of the aforementioned milestone.

In order to ground milestones in observable behavior, programs are encouraged to develop entrustable professional activities (EPAs) for each rotation. EPAs are units of professional practice that can be performed (and observed by faculty) with increasing autonomy and decreasing supervision over time.[26,27] Think of EPAs as essential goals to achieve over training. For instance, on the ward service, a trainee should know how to manage febrile neutropenia and conduct a family meeting; on the hematology consult rotation, a trainee should accurately interpret a peripheral blood smear; in their continuity clinic, a trainee should recognize and manage the toxicities associated with chemotherapy. EPAs can inform multiple competencies as noted in Table 2. The

training programs, under NAS, have the independence to create the types and numbers of EPAs for each rotation.

ASSESSMENT STRATEGIES
Direct Observation

Direct observation provides the most accurate assessment of a learner and provides the opportunity for immediate feedback. Direct observation removes the biases of hearsay, selective recall, or forgetting details that are common in global end-of-rotation ratings. One of the limitations of direct observation is that the rater may observe the learner in only a fraction of their working hours. Direct observation should be made by multiple observers on many occasions, and these should be reviewed by the training program's competency committee.

The 360-Degree Evaluation

Multisource or 360-degree evaluations are another assessment strategy that is valuable in providing evaluation of a learner from multiple raters or sources. Such evaluations are common in industry and gaining acceptance in the assess-

TABLE 2. Linking EPAs to ACGME Competencies

EPA Examples	ACGME Competencies					
	PC	MK	PBL	SBP	ICS	P
Manage neutropenic fevers	X					
Conduct a family meeting	X				X	X
Interpret a peripheral blood smear	X	X				
Manage chemotherapy toxicities	X	X		X		

Abbreviations: EPA, entrustable professional activities; ACGME, Accreditation Council for Graduate Medical Education; PC, patient care; MK, medical knowledge; PBL, practice-based learning and improvement; SBP, systems-based practice; ICS, interpersonal and communication skills; P, professionalism.

ment of physician competencies. A systematic review found that use of such evaluations by an adequate number of colleagues, coworkers, and patients were highly reliable, valid, and feasible.[28] Many competencies can be evaluated using multisource evaluations. For example, trainees can be assessed on their milestones, inpatient care, and communication skills by a wide array of members of the health care team, including peers, ward and clinic nurses, pharmacists, social workers, administrative workers, and by their patients. In addition, these evaluations may also reflect the competencies of professionalism and systems-based practice. Program coordinators can assess professionalism and communication skills.

Unprofessional behavior may be identified by 360-degree evaluations as trainees are unlikely to exhibit this behavior in the presence of a supervising physician. Interestingly, in a study of multisource evaluation of physicians' professionalism, ratings by peers, coworkers, and patients were highly correlated, but did not correlate with self-evaluations.[29] One example of a 360-degree assessment based on the ACGME core competencies is the B-29. It is a validated instrument for identifying unprofessional behaviors and can be used as a feedback tool for physicians to improve behaviors.[30] Like the previously cited study, reliability of multisource ratings depended on an adequate number and type of evaluations.

TEACHING STRATEGIES
Simulation/Standardized Patient Experience

The standardized patient (SP) or patient simulation is an individual trained to act as a real patient in order to simulate a set of symptoms or problems. Standardized patients present a high-fidelity simulation of a real clinical situation.[31] They also provide a standardized presentation of the same patient problem from examinee to examinee in assessment settings.[31] Prior studies of medical students have demonstrated that although real patients are the preferred method for medical students to learn communication skills, experiential techniques such as simulated patients, videotaped interviews, and instructor feedback are more effective than didactic sessions for teaching communication skills.[32] Simulation allows participants to experience the patient in a variety of roles and as often as required in a nonthreatening environment.[33] Despite prior studies indicating anxiety and skepticism associated with performing in front of peers, the feedback on performance skills provided by facilitators, peers, and patient actors broadens the experience for participants and, thus, could increase the learning experience. Back et al have shown that using patient actors does not require that the learners are skilled at acting, but rather enables trainees to learn in their usual role as physicians and introduces them to the value of simulated patients for refining communication skills.[34] Moreover, the use of SPs compared with real patients avoids the ethical conundrums of using real patients and ensures each trainee has the same experience.[35]

Let's return to the milestone mentioned previously: Responds to each patient's unique characteristics and needs.

Although the faculty member might globally note that a trainee is professional, has the evaluator actually witnessed the trainee communicating with the patient in a culturally competent manner and is the trainee able to involve the patient in his or her own care? Although this may occur in the course of clinic or ward duties, it is recognized that such opportunity may not regularly occur. Educators could use simulation/standardization training to inform this milestone in a structured encounter where the trainee discusses end-of-life issues with a patient from a different ethnic or socioeconomic backgrounds. Although this may occur in the course of training, this structured activity allows trained evaluators to observe these behaviors, and provide direct feedback (from both patient and evaluator) immediately at the point of interaction. Examples of such SP/simulation examples to teach this skill can be seen in Table 3.

Trainees would rotate through each example in a half-day session devoted to development of these communication skills. On a resource level, several items will be required including space, funding, faculty who are trained and willing to develop scripts for SP, training for the SP, faculty trained in communication skills and observation to observe and provide direct feedback (ideally several faculty members), and faculty and trainee time to perform these activities. The ACGME now mandates all programs to participate in training using simulation. Thus, the onus remains on the medical educator to plan and perform activities that meet the needs of the learners at each institution.

TABLE 3. Proposed Standardized Patient Simulations to Evaluate Cultural Competencies

Each trainee would rotate through each scenario below:

Standardized Patient 1:	The patient is an African American woman age 85. She is computer illiterate and very involved with her church. She is able to read at an 8th-grade level. She always comes to clinic with a daughter and granddaughter. She has been unable to tolerate previous chemotherapy for her metastatic breast cancer and has already had three regimens for metastatic disease. Discuss best treatment options.
Standardized Patient 2:	The patient is a Latino man, age 48, who is a recent immigrant. He does not speak or read English. He works in the construction industry. He is a smoker. He is now diagnosed with metastatic pancreatic cancer. He does not have family in this country. He does not have insurance. He has lost 30 lbs in the past 6 months and his performance status is 3. Discuss best treatment options.
Standardized Patient 3:	The patient is a Caucasian woman, age 32, from a rural community that is 60 miles from your medical center. She reads on a 4th-grade level. She can play games on the computer. She has three small children. She is married. She is unable to work. The annual household income is less than $15,000. She now has recurrent and refractory acute myeloid leukemia, but is eligible for a clinical trial. Discuss her options.

E-Learning

E-learning is a unique pedagogy in which Internet technology is used to enhance learner knowledge and performance.[36] Educational content delivered via e-learning is rapidly revolutionizing medical education and health care delivery. Educational websites, virtual patient simulations, online problem-based learning, podcasts, and interactive multimedia tutorials are all forms of e-learning.[36,37] Alur et al describe a blueprint for educating health professionals through e-learning that necessitates the development of an educational website that acts as a medium for sharing information while encouraging active learning, critical thinking, and independent and evidence-based learning by the learner.[38] A study evaluating 112 teaching websites in North America, the United Kingdom, and Australia found only 17% of websites ascribed to these principles.[38]

When used appropriately e-learning applications can enhance the efficiency and efficacy of educational interventions,[39] and basic science and clinical educators have begun using e-learning as adjuncts or replacements to traditional in-person courses. E-learning has the capability to result in effective learning, but also offers benefits that a traditional classroom may not offer. These benefits include efficiency,[40,41] flexible scheduling,[40,41] and customized feedback.[42] In addition, e-learning programs can be designed with hyperlinks that allow learners to independently research information and broaden their search to related topics. These attributes are particularly useful in the self-directed, problem-based learning environment, which is valued by practicing physicians. In addition, e-learning is able to overcome barriers of physical distance, allows unlimited viewers and viewing, is easily updated, and allows retention and transfer to new settings.[40-42] Barriers to the use of e-learning include lack of time for the user, dissatisfaction with speed of the medium, technology problems, student support issues, and instructional design.[43,44]

A prior meta-analysis demonstrated that e-learning leads to greater learning than no learning.[45] E-learning also has similar levels of participant satisfaction and equal or greater improvement in knowledge and skills acquisition compared with traditional in-person learning methods.[45,46] Prior studies regarding learning have shown that integration of new material into the learners' previous subject knowledge may be advantageous and result in effective learning.[47,48] Cook and Dupras[49] identified key elements required to develop an effective educational website including performing a needs analysis and specifying goals and objectives, determining technical resources and needs, evaluating and using preexisting software, securing commitment from participants to identify potential barriers to implementation, developing content in close coordination with Web design, encouraging active learning, self-reflection and use by the learner, evaluating the learner and the course, piloting the site, and monitoring the site. Harden and Laidlaw describe the CRISIS model for developing effective continuing medical education. In their model they describe convenience, relevance, individualization, self-assessment, independent learning, and systematic.[50] These frameworks are being used in the development of e-learning modules to ensure best practice.[50]

The Flipped Classroom

Traditionally, medicine has been taught by didactic lectures, from medical school through graduate training. However, the volume of medical knowledge has exploded, and the adaption of technology-based learning has increased in the last decades. In this learning environment, educators have to be more efficient and innovative. The concept of a flipped classroom refers to learners viewing information digitally on their own and using class time for more engaged, case-based learning or simulation, discussion, and/or clarification of concepts. Rather than the teacher delivering the same lecture to all students, students learn the material on their own, at their own pace, and the classroom time is used for actual hands-on teaching.[51] Flipped classrooms and related concepts, including blended learning, a combination of online modules and in-class instructions, have been used successfully in a variety of student rotations (third-year radiology clerkships,[52] fourth-year clerkships,[53] and emergency medicine residency).[54]

Training programs can incorporate flipped classrooms by building a library of digital recordings, PowerPoint presentations, papers, and other online resources that trainees can access before time set aside for interactive in-person discussions. The flipped classroom model allows educators to maximize their in-person learning time to convey critical information to the learner who has achieved some basic understanding before coming to their session. How can this be used in the era of NAS and the milestones? Consider the competency of medical knowledge. Most programs use the in-training exam and their gestalt of a fellow's medical intelligence to evaluate them. Under the milestones, a subcompetency for medical knowledge includes "knowledge of diagnostic teaching and procedures" (MK2). A flipped classroom would allow students to learn online about a specific disease, where risk factors, diagnostic tools, and treatment are reviewed, including the latest clinical trials. In person, they can have a focused case review, discuss appropriate testing, the limitations and indications for tests, and provide time for correct interpretation of tests and possible treatment strategies. Learners are not expected to pass a one-time grade, but rather to be on the appropriate continuum of learning for their level of training. Institutions, through their graduate medical education office, should provide coordinated resources for digital information.

Social Media

Social media has changed the way information is communicated and disseminated. Examples include podcasts, Twitter, and networking communities such as LinkedIn. Podcasting is a form of asynchronous learning where the learner can tune in at their own convenience and listen to talks or discussions. The American Society of Clinical Oncology (ASCO), as an example, uses podcasts where key *Journal of Clinical Oncology* articles are discussed, allowing the reader not only a

greater understanding of the study results, but how these results can be applied in their daily practice. Training programs can incorporate podcasts into their curriculum in a similar fashion. Twitter allows subscribers to send brief updates on topics they believe are important to their followers. An example of a recent tweet is "What are the treatment paradigms for prostate cancer?" that serves as a notice for an upcoming tumor board on ASCO University. ASCO members can tweet on interesting findings that are published or presented at meetings. Networking communities such as LinkedIn or Doximity allow health care professionals to connect with one another and industry partners, view new job postings or promotions, or connect with communities of liked-minded individuals online.

CONCLUSION

With all these changes, this is an exciting time in medical education. With new teaching and assessment strategies and all the technology available to the educator, we can now only ask "How could Tinsley Harrison do it differently?" We are teaching a new generation of students who have the Internet at their fingertips and an application for every indication. In our changing health care environment, with limited duty hours, busy clinics, and overflowing hospitals, adaptation of new assessment strategies and novel teaching strategies will allow for a generation of physicians who may not think like Harrison, but will continue to deliver outstanding patient care.

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Perspectives on Clinical Trials for Gastrointestinal Malignancies

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W e all accept the premise that clinical trials are essential to improving the care and outcomes of those afflicted with cancer. Indeed, without successful enrollment into clinical trials, there would be no new diagnostics or treatments for cancer. Yet, it is often quoted that fewer than 5% of adult patients with cancer participate in clinical trials. The dismal accrual rates have been the subject of many learned reviews. In this article, two academic oncologists, a patient advocate and a cancer survivor/author contribute our perspectives on the problem and have chosen to focus on gastrointestinal cancers in the United States as our example.

THE PROBLEM: THE PHYSCIAN PERSPECTIVE

First, we must ask if the approximately 5% participation rate in clinical trials is accurate, and of whom this 5% comprises. Murthy et al[1] calculated an enrollment fraction of 1.7% in National Cancer Institute (NCI)–sponsored clinical trials divided by the total estimated cancer cases in the United States. Whereas 3.0% of patients age 30 to 64 enrolled in a clinical trial, but only 1.3% of those age 65 to 74 participated. Given that the median age of diagnosis of a gastrointestinal (GI) malignancy is 71[2], it is clear that the majority of patients with GI cancer (i.e., those 65 and older) are underrepresented. In another snapshot of recent accrual, Al-Refaie et al[3] noted that of the 244,528 patients (with melanoma, breast, lung, esophagus, gastric, liver, pancreas, colon, rectum, or anal cancers) in the California Cancer Registry between 2001 and 2008, a meager 0.64% enrolled in a clinical trial. The enrollment rate was even further reduced among blacks compared with whites (0.48% vs. 0.67%, p < 0.05). Of those who did enroll, 97% had some form of health insurance and 3% listed insurance as either none or unknown. During this same period of time, it was estimated that 29.5% of California adults were uninsured.[4] Clearly, lack of insurance has been a major barrier to accrual. In sharp contrast, in 2007, the United Kingdom reported 32,000 patients (14% of the annual U.K. cancer incidence) were enrolled in clinical trials.[5] In 2014, the number of patients enrolled has increased dramatically to more than 60,000.[6]

Even among those who are eligible and insured, access to a trial is not a certainty. Of the 4,617 patients enrolled in a clinical trial[7] at John Hopkins Medicine (2003 to 2008), 628 patients (13.6%) were denied trial enrollment because of refusal of insurance coverage. To date, these challenges remain, and they appear to be mounting given the arduous amount of additional work that is sometimes required of health care providers. With the approval of the Affordable Care Act (ACA), it is expected that there will be increased patient enrollment since insurance providers are required by law to provide for routine patient costs associated with clinical trials.[7]

Recognizing the inefficiencies inherent to NCI-sponsored cooperative group research, the Institute of Medicine prompted a reduction/merger of cooperative groups with the intention of reducing redundancy and expediting the design and conduct of clinical trials.[8] As per the NCI's Operational Efficiency Working Group (OEWG) report, this has made some initial effect in regards to reinforcing investigators to follow a tight timeline.[9] Yet, the reimbursement rate per patient enrolled (approximately $2,000 per patient) has not changed for over a decade. This results in a financial loss to the institution and is an additional disincentive to open and accrue to NCI cooperative group trials. Furthermore, the effect of U.S. government budge sequestration adversely affected all aspects of research development from bench to bedside.[10] With increasing costs of research, largely due to the limitations of drug accessibility, even pharmaceutical-sponsored studies are being referred overseas because of the reduced costs and rapid enrollment compared with the United States. For example, when surveying 20 of the largest U.S. pharmaceutical companies, it is reported that up to one-third of phase III clinical trials are being conducted overseas.[11-13]

Personalized (or precision) medicine adds complexity to clinical trial enrollment. Patients and oncologists are more frequently ordering molecular profiling of tumor samples, with the hope of finding an actionable target. Patients are

seeking treatment that is tailored to their cancer, and they may choose off-label agents as a result of such tests instead of enrollment in a clinical trial. Furthermore, numerous clinical trials are now selecting patients with specific, and often rare, mutations. Accrual to these studies can be very slow and expensive when an investigator has to screen 100 patients to enroll 3 in a disease where the actionable mutation occurs in only 3%.

THE PERSONAL TOLL: THE PATIENT PERSPECTIVE

Access to and the availability of clinical trials are paramount to patients with cancer. To what lengths would you go to save your own life? What would it mean to be told all approved medical treatment options have been exhausted for your type of cancer? From the patient perspective, as much as one would desire to labor under the assumption that "plan A" treatment will cure your cancer, discussing "plan B" could prove beneficial before completion of primary treatment. Initial treatment plans should include long-term strategies for cancer management, regardless of stage at diagnosis. Indeed, initial conversations with an oncologist should include clinical trials, even if no trial is available for that patient at that time. Concern about whether the prescribed treatments will work easily overshadows any quoted statistics. Additionally, efficacy of current treatment regimens is a moot point to the newly diagnosed unless it is 100%. (For example: if a treatment has an 80% efficacy rate, the patient will undoubtedly ask what happens if he or she has a disease that is part of the 20% failure rate.)

Knowledge about available clinical trials offers a sense of preparedness that helps to fulfill a basic human need: safety. Physicians should not assume that patients will know what clinical trial options exist for their disease and thus proactively ask physicians about them if they are interested in enrollment. Even if that was the case, discovering and proficiently navigating clinical trial search engines proves difficult under the best of circumstances. Discussing clinical trial options with patients serves a dual purpose. First, it displays the physician's confidence in clinical trials as a viable treatment option, which serves to nourish the patient's precarious safety needs. Second, rapid and educated decision making is often critical for patients diagnosed with aggressive and/or rare cancers, and this requires proficiency in deciphering the current active clinical trial library. Cross referencing data for trial drugs also would be helpful to patients who want to explore every treatment avenue. Access to clinical trials for patients with any type of cancer— common or rare, primary or recurrent—is vital. The words "you have cancer" are life altering. Coupled with advanced staging or rarity, those words are life threatening. Improved access to and availability of clinical trials with promising drugs or treatment regimens do more than just satisfy enrollment numbers, they offer hope. And hope is essential for patients with cancer.

PROPOSALS FOR IMPROVEMENT: THE PATIENT ADVOCATE PERSPECTIVE

Most patients with cancer are diagnosed in a community setting. It is imperative to create a culture of research in which an oncologist is expected to discuss trials with patients, enroll or refer them when appropriate, and do so with minimum disruption to their practice while taking pride (and perhaps even a marketing advantage) in participating in a larger research effort.[14] Establishing an infrastructure that support trials conducted in the community is essential.

Clinical researchers need to design trials for real-world patients; trials that match the demographics of the disease and trials that can be conducted in a community setting. Eligibility criteria designed for phase I trials of cytotoxic chemotherapy should be simplified and loosened for phase II and III trials, especially for treatments that do not include cytotoxic chemotherapy. Published literature of rare cancers is largely based on retrospective single institution studies or database reviews. Allowing enrollment of patients with select rare diseases into common cancer trials would allow otherwise ineligible patients to have access to treatment and would provide additional prospective data for rare diseases. This methodology has already been accepted by the Gynecologic Oncology Group (GOG); patients with primary peritoneal cancers are allowed to enroll in ovarian cancer trials. GI oncologists have agreed to include gall bladder cancers in trials for cholangiocarcinomas. Therefore, why not include appendiceal and small intestinal adenocarcinomas in metastatic colorectal trials or ampullary tumors in pancreatic cancer trials? Studies can be powered for the primary endpoint of the more common tumor (if necessary). We do not pretend that appendiceal adenocarcinoma is the same as colon adenocarcinoma, yet, in the absence of data, we tend the treat them the same off protocol. Therefore why not gather some data on protocol?

Dramatic improvements in small subsets of molecularly defined lung cancers using targeted therapies have demonstrated the feasibility of this approach. However, will we ever be able to conduct a randomized trial in the 10% to 15% of gall bladder cancers that are HER2/*neu*-positive?[15] The proliferation of gene sequencing and other assays intended to detect specific molecular vulnerabilities in cancer have resulted in too many "one-off" experiments. That is, a nonprotocol patient who gets a test result suggesting that a drug might be useful, based on either preclinical experiments or clinical experience in another disease, might then respond or not respond to that drug, but that data is never (or seldom ever) added to a database. The pharmaceutical industry and the NCI have created basket trials that are agnostic of tumor site of origin and accrue to treatment arms based on molecularly defined targets. These basket studies are methods of discovery and not likely paths to U.S. Food and Drug Administration approval of a drug for a specific target.

Disease-specific, molecularly targeted therapies can only occur in more common cancers. BATTLE and ISPY trials for lung and breast cancer, respectively, offer disease-specific options in targeted therapy design that could be adopted in

colorectal cancer. Indeed there are plans to open an NCI-sponsored ASSIGN trial to test targeted agents in molecular subsets as second-line therapy of metastatic colon cancer. Although critically important to finding and validating new targeted agents for colorectal cancer, the difficulty in getting such a trial activated is daunting and would still leave the many other GI sites lacking this level of trial access.

Although studies have shown that the cost of care for patients in cancer clinical trials is not substantially greater than the costs of routine care, insurance[16] companies have not universally embraced clinical trials as a component of standard care for patients with cancer. Legislative efforts such as SB37 in California have mandated that insurers pay for the routine care costs for patients to participate in a clinical trial and cannot deny access to a trial. However, loopholes exist. Nearly 30% of California adults are uninsured, which makes us hopeful that ACA will provide coverage for and access to clinical trials for those who were previously uninsured.

In the 2014 *ASCO Educational Book*, the use of social media to improve clinical trial accrual was discussed.[17] Another creative use of the Internet is crowd sourcing for feedback on how to improve the design and accrual of a particular clinical trial. Leiter et al[18] used a Web-based platform that allowed participants to comment on the design of a clinical trial using metformin in prostate cancer. Hyperlinks were posted to social networking sites. The platform was available for 6 weeks, and this crowd-sourcing exercise resulted in 9 changes to the protocol, 4 of which were major changes. Certainly the potential of the Internet and social media to improve awareness of and accrual to trials remains relatively untapped.

Patient advocacy groups may positively influence clinical trial accrual. The Pancreatic Cancer Action Network (PANCAN) has reported that although only 3% of patients with pancreatic cancer in the United States enroll in trials, 16% of those patients have called a help line to participate in clinical trials. Although an obvious selection bias favors patients and families who want more information, we would contend that the effect is real and that PANCAN's advocacy for trials has an effect, even if not five-fold in magnitude. Sadly there are relatively few support groups for other GI sites and none of the size and financial power of those for breast and prostate cancer. However, if there could be a coalition of GI-minded advocacy groups to make clinical trial accrual a priority, we might hope that a similar improvement in accrual might occur.

Trials such as BATTLE, ISPY, and, hopefully, ASSIGN should be encouraged and supported. Novel design methodologies might make such trials easier to complete with fewer patients needed to achieve clinically relevant endpoints. The PANGEA trial[19] for gastroesophageal cancers is one such novel design that merits further attention.

In GI malignancies, the only molecular tests that have been validated to affect patient outcomes would be *RAS* testing for metastatic colorectal cancer, HER2/*neu* for metastatic gastric cancer, and microsatellite-instability (MSI) for stage II colon cancer. All other molecular tests should be the subject of further study. The plethora of molecular testing for cancer approved under the Clinical Laboratory Improvement Amendments of 1988 regulations is not linked to any accountability. Patients and oncologists alike, in good faith, may order such tests to be told that a drug seems like a good match for the genetic alteration "y" in the patient's tumor, but rarely are there data to support a clinical benefit of receiving that drug in that particular setting. We should find a way to encourage/mandate that any physician who orders a molecular profile (outside the confines of the examples listed above) should also obtain consent from the patient to review and discuss the results of the profile, and if a treatment is administered purely on the basis of the molecular testing, that the response to that therapy is registered anonymously in a database available to all researchers. The establishment of such a database could be a source of discovery and aid in the design of clinical trials to validate promising results. Currently, the patient may or may not respond, but that information is lost to a future generation of patients with cancer who might have benefited from that knowledge.

CONCLUSION

As academic oncologists, we know how rigorous the scientific methodology must be to prove a treatment is beneficial. As a community of providers, patients and families, we know all too well the emotional and physical toll a cancer diagnosis takes. The price of neglect is too high. Together we must find ways to increase access, improve design, and speed completion of clinical trials—for the good of all.

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I Will Recommend a Clinical Trial—If I Can

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You have completed your examination and have left the patient's room to let her get dressed while preparing to sit down with her and her partner to discuss her diagnosis, stage, prognosis, and treatment recommendations. With the patient's permission, a second-year medical resident will sit in on this discussion. As you wait, you run through what you are planning to say, especially about her standard treatment options and about a clinical trial for which she appears to be eligible—a randomized study that could answer important questions about the treatment of her disease. You tell the resident that the doctor's role in suggesting and explaining a study to a patient is vital, even though the research staff will do much of the work if the patient agrees to consider the study. But you can only succeed if you try. Albrecht et al, studying interactions between oncologists and patients and their families at two comprehensive cancer centers, found that clinical trials were offered to patients only 20% of the time, but, when offered, 75% of patients agreed to participate.[1] In a telephone survey of 1,000 adults, 32% of responders said they would be very willing to participate in a cancer clinical trial if asked and another 38% indicated that they would be inclined to do so.[2]

Unfortunately, scenes like this could well become much less common for many medical oncologists, especially those who work at smaller academic cancer centers, community hospitals, and private practices, where the vast majority of Americans receive their oncologic care. Many sites that have been involved in clinical research for decades are finding it increasingly difficult to gain access to clinical trials that they can offer to more than a minute fraction of their patients. Why is this? Certainly there is no dearth of important questions to address regarding the management of many common cancers. In the past, many of the larger trials in which patients participated originated with the site's cooperative group; the creation of the Clinical Trials Study Unit (CTSU) offered the opportunity to enroll patients on phase II and III studies conducted by other groups. Many institutions and practices have supported their staff's participation in the groups, covering the costs of membership and travel to attend group meetings and accepting a reduction in "productivity" so that the site can contribute to the research effort.

You know that this part of the conversation can be disconcerting for the patient; she was referred to you because of your knowledge and experience, not to have such an important decision made by a computer, by a flip of a virtual coin. Why open this can of worms? You are already 40 minutes behind schedule, and the study discussion is bound to add at least 30 minutes to this visit. It is certainly not for the money; with the exception of a few well-funded pharmaceutical company–sponsored trials, your protocol office actually loses money on a per-accrual basis. It is not for the "glory"—there is no way your site will enroll enough patients on this large study to be given authorship credit, and, in the academic scheme of things, clinical research is a poor relation. You know the statistics, which you share with the resident—how few patients are candidates for available trials despite efforts to liberalize eligibility criteria, how few are offered the chance to be part of a trial, how few agree to participate (less than 5% of adult patients with cancer enroll in clinical trials, in comparison to more than 60% of children with cancer), and how many studies fail to meet accrual goals or take years longer than planned to answer the important questions they address. How many axillae were unnecessarily dissected because it took so long to complete ACOSOG Z0011?

The accomplishments of the U.S. cooperative groups in advancing the understanding of and improving outcomes for many different types of cancer should not be underestimated (see summary by Schilsky[3]); if you scan the lists of plenary and oral abstract presentations at the American Society of Clinical Oncology's Annual Meetings, or any other major national meeting over the past 2 decades, you will see ample evidence of their effect, despite being level-funded since 2003 (which has the effect of reducing available funding by a few percent every year, given inflation), and over the past few years, many presenters have reminded us of this origin for their practice-changing trials. Still, there is no doubt that they could have been more productive and efficient and that there were costs associated with their conduct that could be re-

duced, and thus it was no surprise when the Institute of Medicine report "A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program" produced at the request of the National Cancer Institute (NCI), recommended major changes designed to improve the cooperative group system.[4] Many in the cooperative groups applauded the recommendations, which included providing additional funds to help the groups modernize systems and increase patient and physician incentives.

You know that the patient and those closest to her simply want to know what is best for her, not for some faceless stranger in the future, and admitting that we do not know what is best is difficult. You know that random selection, fear of receiving a placebo, and fear of developing any of the long list of potential side effects listed in the consent form (even if the list of side effects for the standard treatment is just as long) are among the greatest barriers to clinical trial participation.[5] As you explain to the resident, it is a delicate balance. If you come across as too enthusiastic about the experimental approach, it may seem that you are trying to "sell" the study and could lead the patient to believe that she would be getting inferior treatment if she is randomized to the control arm, so why do not you just give her the "better" treatment? You remind yourself of how often what some experts were sure was a major advance—such as bone marrow transplants for breast cancer and MACOP-B instead of CHOP for diffuse large cell B-cell lymphomas—proved to be no better and only more toxic when the randomized trials were finally completed.

Instead of using the Institute of Medicine report to support their efforts to lobby Congress for additional funds for the clinical trials program, the NCI leadership chose a different direction. While announcing plans to support upgrades in information technology, centralized laboratories, and biospecimen tracking, they compelled the existing cooperative groups to consolidate and announced reductions in overall accrual, achieved in part by eliminating sponsorship of studies with an accrual goal over 1,000. The NCI's decision essentially leaves the field of larger, randomized clinical trials to the pharmaceutical companies, which suggests that the only studies done will be those designed to support the approval of costly new therapies. The NCI's stated intent is to use its limited funds to sponsor early phase trials designed to test biomarker-driven hypotheses,[6] which by definition will be limited to the small subset of patients whose tumors test positive for a potentially targetable mutation. This strategy is designed to look for large differences in outcomes instead of incremental improvements rendered statistically significant by sheer size. While not questioning the value of this approach for hypothesis-testing in biologically defined patient subsets, it leaves scant resources to answer clinical questions that will not benefit a pharmaceutical sponsor, such as comparing two regimens comprised of generic drugs or determining if a biologically defined patient subgroup might do better without or with briefer exposure to a costly and/or toxic treatment that is the current standard of care.

You dread hearing "I do not want to be a guinea pig," because it makes you want to scream that none of your patients are guinea pigs and that giving a patient an investigational treatment—no matter how promising—before it has been proven to be more effective and/or less toxic in with a well-designed and well-conducted clinical trial would be inappropriate. Instead, you calmly tell them that it is only because patients like her agreed to participate in past studies that we have been able to define our current, yet admittedly imperfect, standard treatment. And when they ask you, "What would you do if she were your wife or partner?" you can honestly answer that you would support participating in the study. You can also say, to patients who are members of an ethnic minority, that it is important that a variety of ethnic groups take part in the study, to make sure that its results are broadly applicable and to identify any differences in disease biology and treatment effect; close to 90% of patients who enroll in NCI-sponsored clinical trials are white, of whom less than 6% are Hispanics/Latinos.[7] There may be the added challenge of overcoming suspicions as to the beneficence of the clinical trials process based on a few infamous historic precedents, such as the Tuskegee syphilis study.

In addition, except for the 30 Lead Academic Participating Sites (LAPS), which under the new system receive additional funding to support their clinical trials program, financial support for participating in NCI-sponsored studies remains inadequate. After spending the last 20 to 30 years training the next generation of medical oncologists, radiation oncologists, surgeons, etc., to revere the randomized clinical trial and encouraging cancer programs to hire research staff, the rug is being pulled out from under their feet. To maintain these research programs will require even greater dependence on pharmaceutical company–sponsored studies. To expand and diversify their study portfolios, cooperative groups have established or expanded affiliated "foundations," which hope to compete with contract research organizations with the promise of improving the science associated with these trials; it is too early to know how successful these efforts will be. And although many of the pharmaceutical companies have been generous in supporting investigator-initiated studies that may never lead to drug approval or label expansion, to what extent this will continue is unclear.

You will have to explain that participating in a study may require additional office visits, blood tests, scans, questionnaires, blood and/or tissue samples, in some cases even additional biopsies, for correlative research studies. New ways of analyzing patients and their cancers promise to revolutionize our understanding of and, hopefully, treatment for her cancer, offering the hope of truly personalized oncology, but only if studies are completed that demonstrate a correlation between these findings and patient outcomes. You comment to the resident that maybe we should make it easier to enroll in studies, or harder to refuse them. In some countries the only way to get a standard treatment is to participate in a study, but fortunately that is not often the case in the United States. Of course it is easier to accrue if the only way to get a promising investi-

gational treatment is on trial, such as in the adjuvant trastu-
zumab studies. Would it not be easier if consent forms were not
20 or more pages long, with interminable lists of potential (if
rare) side effects? Do we really expect our patients to read and
comprehend such a lengthy document, even if (supposedly)
written at an eighth-grade level?

So what can or should we do about the direction of the U.S. clinical trials system? I agree with those who have spoken in favor of a publicly funded clinical trials system,[3,8] and I do not expect or want the NCI leadership to reverse direction on the value of precision medicine trials. Although that initiative is important, I would like to believe that we can walk and chew gum at the same time; that is, conduct those smaller-focused studies without relinquishing the ability to pose pertinent questions that require much larger trials to answer. So we should lobby our congresspeople and senators to increase funding to the National Institutes of Health that is earmarked to the cancer clinical trials program, perhaps even specified to go toward larger trials, some of which may be designed to determine if we can reduce the toxicity and cost of treatment without reducing its efficacy. We could make the argument that a relatively small investment in such studies could potentially save the system a great deal more. As an alternative to government spending, we should encourage philanthropies like the Conquer Cancer Foundation to consider trying to enlarge their donor base by offering individuals and foundations the opportunity to step into this gap and help fund large, simple trials that address important questions. Such trials could be run on, relatively speaking, a shoestring budget, with sites making up for low per-case funding with higher accrual, and reducing costs by collecting only key outcomes and toxicity data and minimizing costs by holding study group meetings via the Web.

We could even explore creating a virtual tissue bank, where samples are held at the treating institutions and sent to a designated research facility only when requested.

It boils down to understanding the importance of your role
as the patient's physician and advocate, even if it is the first
time you have met. If you truly believe that participating in the
study could be her best option, you can also acknowledge that
an important reason why you take the time to do this is so that
when you, or another physician, perhaps even that resident, sit
down with a patient like her in 5, 10, or 20 years you will be
able to say whether treatment A is better, equivalent to, infe-
rior to, or less or more toxic, than treatment B. In the end,
when the results of this study have been presented and pub-
lished, you can both be proud to have been part of the process.

That is, assuming you still have sufficient access to trials to offer to her and your other patients.

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BREAST CANCER

Challenging Issues in Metastatic Disease

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Precision Medicine for Metastatic Breast Cancer

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OVERVIEW

Genomic studies have shown that large numbers of candidate targets are observed in breast cancer. Nevertheless, only a few of them are validated as relevant targets in clinical studies. Estrogen receptor (ER) and HER2 expressions could be associated with a level I evidence. Beyond ER and HER2, *BRCA* and *PIK3CA* mutations (when targeted with alpha-specific PI3K inhibitors) could be considered as promising targets in breast cancer since they have been associated with objective responses in phase I/II trials. In addition to these four molecular alterations, several others have shown promising results in preclinical studies and are being investigated in clinical trials. These genomic alterations include *AKT1*, *ERBB2*, and *ESR1* mutations. These considerations highlight the lack of evidence for using multiplex technologies to individualize therapy in metastatic breast cancer. Sequencing multiple genes to treat metastatic breast cancer is very promising but should be done in the context of clinical trials, either to enrich phase I/II trials in patients with genomic alterations or to show medical usefulness of new biotechnologies like next-generation sequencing (NGS). Although most current approaches of precision medicine are aiming at targeting drivers, additional applications could be developed in the future. This includes the identification of DNA repair deficiencies, mechanisms of immune suppression, and identification of minority lethal subclones. Finally, one of the very promising applications of genomics for metastatic breast cancer is the identification of pathway activation or defects at the individual level. For example, gene expression and single nucleotide polymorphisms (SNP) signatures are being developed to detect kinase (such as mammalian target of rapamycin [mTOR]/CDK4) activations or DNA repair deficiencies.

Molecular studies have shown that breast cancer includes a large number of subgroups defined by the presence of a specific genomic or protein alteration. ER expression was the first validated target in breast cancer, leading to the optimal development of endocrine therapy.[1] In the late 1990s, HER2 overexpression was validated as a target and was shown to be a predictive biomarker for the efficacy of trastuzumab.[2] During the 2000s, genomic analyses based on gene expression arrays suggested that breast cancer could be divided into four different subgroups: luminal A, luminal B, HER2-enriched, and basal-like.[3-5] Further studies have suggested that basal-like cancers can be subdivided into six subgroups.[6] More recently, studies on NGS have suggested that approximately 40 genomic alterations can be found in primary breast cancers.[7,8] Overall, this introduction emphasizes that each single breast cancer presents a specific molecular profile and specific molecular mechanisms of cancer progression. Parallel to the advances in the understanding of disease biology, several advances in technology could dramatically change patient care. Indeed, it has been shown that high-throughput DNA sequencing together with comparative genomic hybridization (CGH; copy number analyses) can be performed robustly in the clinical practice.[9,10] This has led to the development of precision medicine that involves multiplex molecular analyses to identify molecular mechanisms of cancer progression in each individual in order to improve treatment. In the following review, we present the current state of this approach in metastatic breast cancers (mBC). Several technologies are available to identify genomic alterations in individuals. First, sequencing allows for the detection of mutations. Sanger sequencing, the original method of sequencing, is an approach that allows analysis of only a few genes at the same time. NGS allows sequencing large number of DNA bases in a single run. This latter technology allows multigene sequencing for precision medicine purposes. In some specific platforms and conditions, NGS can also allow quantifying gene copy numbers, although CGH array or fluorescence in situ hybridization analyses are usually better for this purpose. Finally, gene expression array and reverse transcription polymerase chain reaction quantify gene expression. More recently, RNA sequencing is being developed to assess gene expression, translocations, and mutations.

LEVEL OF EVIDENCE SCALE FOR DRUG TARGETS

NGS and other high-throughput technologies analyze several hundred or thousands of genes in the same assay. These technologies can identify many genomic alterations in each patient. Nevertheless, only a few of them are truly implicated in the disease progression. A level of evidence scale that ranks

targets according to their relevance has been developed to facilitate interpretation of these high-throughput assays, better communicate results to patients, and prioritize research needs.[11] Level I evidence includes molecular alterations that have been shown to be validated targets, either based on phase III trials or several large phase I/II trials. Level II evidence includes molecular alterations associated with response to treatment in small or unique phase I/II trials. Level III molecular alterations include those that have been considered as promising targets based on preclinical studies. Finally, level IV evidence includes genomic alterations that are selected based on bioinformatics analyses only, without biologic studies to support them. This level of evidence scale also makes a difference according to whether the molecular alteration has been investigated in the same disease and whether studies included negative controls (evidence that patients without the alteration do not derive benefit from the targeted therapies). This level of evidence scale does not evaluate the medical usefulness of targeting the molecular alteration (benefit as compared with standard of care), but the antitumor activity obtained by targeting it. In the next sections of this article, we will use this level of evidence scale to classify molecular alterations in breast cancer. From this analysis, we will further discuss the current positioning of multiplex assay to treat patients with breast cancer.

MOLECULAR TARGETS AND THEIR RESPECTIVE LEVEL OF EVIDENCE IN BREAST CANCERS

Molecular alterations can be divided between drivers, mechanisms of resistance, mutational process and DNA-repair defects, immune alterations, cell death, angiogenesis, and metabolism. These latter three systems will not be discussed in the present article. The list of the most investigated molecular alterations and their level of evidence are reported in Table 1.

Oncogenic drivers can be defined as molecular alterations involved in malignant transformation and cancer progression. Targeting a driver is expected to lead to tumor shrinkage (known as oncogene deaddiction). As mentioned in the introduction, the two historic drivers include ER expression

KEY POINTS

- Only a few molecular alterations are validated as targets in breast cancer (specifically ER and HER2 expression).
- Driver identification in breast cancers includes DNA-based analyses but also detection of pathway activation and dependency (e.g., ER, mTOR, and CDK4).
- Driver identification is not the sole application of genomics to personalize therapy for metastatic breast cancer.
- There is no evidence that using multiplex genomic testing for metastatic breast cancer improves outcomes.
- Ongoing trials are evaluating the medical usefulness of next-generation sequencing in metastatic breast cancers.

TABLE 1. Potential Applications of Genomics for Metastatic Breast Cancers

Application of Genomics	Optimal Technology	Targets	Level of Evidence Associated with the Target[11]
Drivers (DNA)	Next-generation sequencing if multiple genes validated	ERBB2 amplification	I
		PIK3CA mutations	II
		AKT1 mutations	III
		ERBB2 mutations	III
Drivers (RNA/ proteins)	Gene expression Phosphoprotein assays	ER expression	I
		mTOR activation	ND
		CDK4/6 activation	ND
Lethal subclone	Ultra-deep sequencing Circulating DNA	ESR1 mutations	III
DNA repair	Targeted sequencing Whole-exome sequencing SNP arrays	BRCA1/2 mutations	I/II
Immune system	Whole-exome sequencing RNA sequencing	PD-L1 overexpression	ND
		Neoantigen	

Abbreviations: ER, estrogen receptor; mTOR, mammalian target of rapamycin; ND, not determined; PD-L1, programmed death ligand 1.

and *ERBB2*-amplification. These two targets are associated with level I evidence. Additional candidate molecular alterations are being investigated in breast cancer. These alterations should be divided between DNA-based assays and pathway-based assays. At the DNA level, there are between 10 to 20 genomic alterations that are currently the targets of drug development.

PIK3CA mutations are observed in approximately 25% of breast cancers, mainly those with ER or HER2 expression.[12] PI3K activates AKT1 that subsequently activates mTOR. AKT1 also interact with pathways that do not relate with mTOR, including FOXO, BAD, and GSK3. Several drug families target PI3K/AKT/mTOR pathways, including mTOR inhibitors, AKT inhibitors, nonselective PI3K inhibitors, and alpha-selective PI3K inhibitors. In an ancillary study of the BOLERO2 trial, *PIK3CA* mutations were not predictive for the efficacy of mTOR separate inhibitors in ER-positive/ HER2-negative breast cancer.[13] Nonselective PI3K inhibitors target most of the PI3K subunits and thus present a narrow therapeutic index. These drugs can therefore achieve modest PI3K inhibition. This could explain why nonselective PI3K inhibitors have shown mitigated results in phase II randomized trials.[14] Conversely, alpha-selective inhibitors are very potent inhibitors of alpha subunit, a major player of PI3K activity in cancer. Interestingly, phase I studies using alpha-selective PI3K inhibitors have shown extremely encouraging results in patients who with *PIK3CA* mutations, suggesting that PIK3CA mutation could be a relevant target in mBC.[15,16] This genomic alteration should be ranked level IIa. Activating *AKT1* mutation is the other genomic alteration located in

the pathway. First, *AKT1* mutations occur in approximately 3% of breast cancers. These alterations are oncogenic in preclinical models and have been associated with objective response to mTOR inhibitors in molecular screening programs.[10] Ongoing studies are investigating the efficacy of AKT inhibitors in patients with this genomic alteration. Although some retrospective analyses suggest oncogene deaddiction in patients with *AKT1* mutations, this target is still considered to be a level III target.

FGFR1 amplifications occur in approximately 10% of breast cancers, mainly those with ER expression. This alteration has been associated with very promising results in preclinical studies.[17] Nevertheless, treatment with highly specific and bioactive FGFR inhibitors failed to demonstrate antitumor activity in phase I trials.[18] Interestingly, multikinase inhibitors like lucitanib were associated with promising antitumor activity in patients presenting *FGFR1* amplifications,[19] but whether this antitumor activity relates to FGFR inhibition is unclear. *FGFR1* amplification could be associated with level III evidence as a target. *CCND1* is amplified in approximately 15% of breast cancers. This amplification is not clearly associated with CCND1 expression, and clinical studies have failed to validate that CCND1 amplification are relevant targets in breast cancer.[20] Finally, the last interesting target located on tyrosine kinase is *ERBB2* mutations. These mutations have been shown to be activating mutations and to be associated with antitumor activity of neratinib, a HER2 inhibitor.[21] Phase II trials are ongoing. This target is currently considered as level III evidence but could jump to level I if consistent studies report high levels of antitumor activity for neratinib in this genomic segment.

Besides alterations at the DNA levels, assessing pathway activation and dependency could provide relevant information about driving forces of cancer progression. To illustrate, ER expression drives cancer progression in ER-positive breast cancer, although no alteration is usually detected at the DNA level. This emphasizes the relevance of assessing pathway activation in breast cancer. The Cancer Genome Atlas data have suggested that PI3K/AKT/mTOR and CDK4/Rb pathways are the two most relevant targetable pathways in breast cancer. Gene expression signatures could provide information about activation status of these pathways, together with assessment of phosphoproteins. For example, in the BO-LERO3 trial, biomarker studies showed that activation of mTOR (specifically PS6K) is associated with high sensitivity to everolimus.

Emergence of lethal subclone is a well-described mechanism of resistance to targeted therapies. In patients with lung cancer, it has been well documented that T790M mutations, although the minority at the time of diagnosis, become predominant after resistance to EGFR inhibitors.[22] In breast cancer, a similar phenomenon is being observed with *ESR1*. *ESR1* is the gene that encodes for ER. Although less than 1% of early breast cancers present mutations, it is considered that between 10% to 30% of breast cancers resistant to aromatase inhibitors will have a hotspot mutation thus leading to ligand-independent activation of the receptor.[23,24] It has been suggested from preclinical works that high-dose fulvestrant could present some antitumor activity in this subset of patients. Several new ER degraders like GDC-0810 are being developed in this setting (NCT01823835). Until now, this target is classified level III. There are several questions surrounding this genomic alteration that could have some clinical influence. First, as opposed to T790M, this mutation has not yet been reported in a minority subclone in a primary tumor. Finding the *ESR1* mutation in a minority clone in a primary tumor would open the path for the development of ultra-deep sequencing to detect them and potentially treating them very early during the disease course. Second, the use of circulating DNA could help detect these mutations during the disease course and treat them early. Finally, one study has suggested that *ESR1* mutations could be associated with very poor outcome. If validated, this finding would suggest that this genomic segment would deserve some fast-track approvals based on phase II data.

The third application for genomic tests is the identification of DNA repair defects and mutational processes at the individual level. Identifying DNA repair defects could lead to administration of personalized synthetic lethality strategies or specific genotoxic agents. The best example in breast cancer is provided by *BRCA1* and *BRCA2* mutations. When biallelic, *BRCA1* and *BRCA2* mutations and/or loss lead to homologous recombination deficiency and genomic instability. *BRCA1/2* mutations have been associated with sensitivity to PARP1 inhibitors (synthetic lethality) and DNA alkylating agents (genotoxic).[25] Interestingly in these trials, patients without *BRCA1/2* alterations did not present a similar degree of antitumor activity as compared with patients with mutations. Based on these consistent data from phase III and large phase II programs, *BRCA1/2* mutations as drug targets have a level I evidence.[11] The controversy in this area is more about how to position each therapeutic strategy (PARP1 inhibition and DNA alkylating agents) and to show medical usefulness over standard of care, rather than whether *BRCA1/2* mutations constitute a target per se. The second controversy is about whether some functional tests evaluating homologous recombination deficiency (HRD) could have better performance than detecting *BRCA1/2* mutations. HRD tests could have better performance either by selecting the right patient with the *BRCA1/2* mutation or by identifying patients with BRCA1/2 wild-type who present with HRD. When assessed retrospectively, the HRD test developed by Myriad was not associated with a differential sensitivity between platinum and docetaxel. The HRD test developed by Clovis has been associated with sensitivity to the PARP inhibitor rucaparib, even in the absence of *BRCA* mutation.[26] An ongoing phase II trial (RUBY) is testing whether rucaparib could present antitumor activity in patients with BRCA1/2 wild-type who present a high HRD. Beyond HRD and BRCA, assessing other DNA repair genes or pathways could allow expanding the array of patients who could be eligible for synthetic lethality strategies. ATM and ATR mutations are observed in approximately 2% of breast cancers and could define a subset of patients eligible for synthetic lethality approaches. In terms of pathways, several studies have suggested that the mutational pattern detected by whole-exome sequencing could allow for defining which DNA repair pathway is

altered in each individual.[27] This could potentially lead to the use of whole-exome sequencing to individualize synthetic lethality approaches for patient treatment.

Finally, the fourth potential application field of genomics to individualize therapy is immunology. Genomics could allow detecting neoantigens and expression of ligands for immune checkpoints,[28] but also test the competence of the cancer cell to present antigens and to be killed. Recent data obtained in metastatic triple-negative breast cancer suggest that anti-PD-1 antibody could present some antitumor activity.[29] Finally, genomic tests could evaluate whether the host could generate an antitumor immune response following immunogenic cell death.[30] For example, *TLR4* polymorphisms confer lack of immunogenicity and have been associated with resistance to anthracyclines in patients with breast cancer.[30]

CLINICAL DEVELOPMENT OF PRECISION MEDICINE IN METASTATIC BREAST CANCER: WHICH TECHNOLOGY? WHICH SAMPLES? WHICH TRIALS?

As discussed in the previous section, there are large numbers of applications for genomics to better treat patients in the metastatic setting. Each application deserves a specific technology and it is important to define which technology will be developed for which purpose. Current approaches of precision medicine aims at identifying drivers at the DNA level. For this purpose, sequencing is the best technology. Whether sequencing should be based on Sanger technology or should consist in NGS depends on the number of genes to be tested. An important aspect of breast cancer is the high number of copy number alterations that could potentially drive cancer progression. Assessing gene copy numbers requires fluorescence in situ hybridization technology for a single or a few genes, or CGH/SNP arrays for a large number of genes. Interestingly, some centers can now robustly assess copy number using NGS technology.[9] This therefore makes this technology a preferred choice for clinical research programs that aim to identify drivers in mBC. Alternatively, circulating DNA could be useful when biopsies are not feasible. As mentioned previously, assessment of pathways activation could be done by gene expression arrays, reverse transcription polymerase chain reaction, or phosphoprotein assays. Other technologies could be dedicated to specific purposes of clinical research. First, ultra-deep sequencing could be an interesting approach to detect minority clones, and circulating DNA could be an interesting approach to detect the appearance of resistance. SNP array could be interesting to quantify HRD. On a long-term perspective, one could argue that the best approach to personalize therapy will be to apply whole-exome sequencing to hard-to-treat mBC. Whole-exome sequencing offers the advantage of detecting both drivers, DNA repair defects and neoantigens.[28] Finally, RNA sequencing could offer the advantage of detecting pathway activation and target expression.

One field for controversy is which sample should be used for target identification in patients. Primary tumors offer the advantage of being accessible and not requiring additional biopsies. Nevertheless, several studies have shown that targets can be lost or gained during the disease evolution.[31] More recently, evidence has been reported that targets acquired during the disease course—although not trunk alterations— could drive cancer progression.[32] This emphasizes the need to assess genomic and molecular targets at the time of treatment decision and start. Assessing cancer biology at the time of treatment decision would need to perform biopsies of metastatic sites. Whenever this is feasible, biopsy of metastatic sites should be the priority since it allows assessing genomic alterations but also RNA and protein expression together with immune markers. Nevertheless, if the tumor site is difficult to biopsy or in case of bone disease, circulating DNA could be a possible alternative.

Until now, there has been no data to support the use of DNA- or RNA-based technologies in daily practice for patients with mBC. Several nonrandomized trials have been performed but they did not provide a clear picture about the potential medical usefulness of precision medicine for breast cancer. In the SAFIR01 trial,[10] approximately 28% of the patients presented evidence of antitumor activity but only 10% had an objective response. These numbers align with phase I/II trials that tested drugs without molecular selection. In a clinical trial testing gene expression, Von Hoff et al reported that a group of patients had their progressive-free survival prolonged under genomic-based therapy.[33] Nevertheless, this trial did not have a control group with patients treated with the same treatments but not driven by genomics. Outside of these two trials, there is no large study reporting efficacy of genomics in mBC, and therefore, with the exception of prospective clinical trials, multiplex approaches cannot be recommended for routine practice.

The next question is how to provide evidence that the use of genomics improves outcomes in patients with mBC. There are two possible strategies to address this question. The first strategy consists of prospectively validating each target in large clinical trials. This strategy is currently being used in most of the clinical programs in breast cancer. For example, HER2 inhibitors are being developed in patients with ERBB2 mutations, PI3K inhibitors are being developed in patients with PIK3CA mutations, AKT inhibitors in patients with AKT1 mutations, and so on. This approach will lead to the clinical validation of several genomic alterations. Once the number of such genomic alterations is large enough, companion diagnosis will very likely switch from Sanger single-gene sequencing to NGS. The second approach will consist of the clinical validation of a multiplex approach. In this design, the trial does not aim to validate each genomic alteration, but to test the hypothesis that using a multiplex technology improves outcomes. For example, the SAFIR02 trial (NCT02299999) is testing the hypothesis that use of NGS and CGH arrays improves outcomes compared with standard of care.

MOVING TO RATIONALE COMBINATIONS

As previously mentioned, breast cancer is a complex disease in which each patient could present several altered genomic alterations and pathways. Therefore, there is a strong rationale to

combine drugs in the era of molecular medicine. There are three possible ways of combining drugs. First, drugs can be combined based on the presence of multiple genomic alterations. It has been suggested that multiple genomic alterations on drivers could be associated with resistance to therapy.[34] Combining drugs that target different genomic alterations could therefore lead to antitumor activity. This is the rationale to combine HER2 and PI3K inhibitors in patients with *ERBB2*-amplified, PIK3CA-mutated BC. The second rationale to combine therapies would be to target molecular processes in different systems. For example, *ERBB2*-amplified BC is associated with a high level of PD-L1 expression and PD-L1-induced immune suppression. There is therefore a rationale to combine HER2-inhibitors and anti-PD-1 in patients presenting *ERBB2*-amplified and PD-L1-induced immune suppression (PANACEA; NCT02129556). Finally, other combinations will aim at avoiding cancer cell adaptation. For example, cancer cells presenting a *PIK3CA* mutation can further adapt to PI3K inhibitors through CDK4 or mTOR activation. This provided a rationale to evaluate triple combinations therapy.

CONCLUSIONS AND PERSPECTIVES

A high number of gene or molecular alterations could be considered as actionable in breast cancer. Nevertheless, only a few of them (ER, HER2 expressions, and—to a lesser extent—BRCA and PIK3CA mutations) are currently validated as relevant targets. There is therefore no robust evidence that using a multiplex technology in mBC improves patient outcomes. Nevertheless, this approach could allow for accelerated drug development by detecting patients with genomic alterations and driving them to phase I/II trials. The current approach to validating genomics for mBC consists of testing drug efficacy in each genomic segment by validating each molecular alteration one by one. Since most of these genomic alterations are rare, there is a need to develop very large molecular screening programs. Several international screening programs have been set up recently including the AURORA program, developed by Breast International Group. Alternative development of precision medicine could consist of evaluating the overall effect of sequencing technologies in the whole population of patients with breast cancer, independently of each single alteration. This approach is being used in the SAFIR02 trial. Finally, one of the major challenges in the future will be optimally to implement these new technologies to secure access to innovations for all patients. To achieve this goal, the Institut National du Cancer has set up 28 public genomic centers in France that have a goal to offer access to genomic tests for free to all patients with cancer. This model, initially based on Sanger sequencing, is currently moving to NGS.

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Surgery or Ablative Radiotherapy for Breast Cancer Oligometastases

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OVERVIEW

Precisely focused radiation or surgical resection of limited metastases resulted in long-term disease control and survival in multiple studies of patients with oligometastatic breast cancer. The integration of these ablative techniques into standard systemic therapy regimens has the potential to be paradigm shifting, leaving many patients without evidence of disease. Although an attractive treatment option, the utility of these therapies have not been proven in controlled studies, and improved outcomes may be because of patient selection or favorable biology alone. Ongoing studies continue to refine radiation techniques and determine the role for ablative therapies in the management of patients with metastatic breast cancer (MBC). Additionally, patient selection for metastasis-directed therapies is based on clinical criteria, with many not benefiting from therapies that may have substantial toxicities. Recent reports are beginning to uncover the biology of oligometastatic cancer, but much work is needed. Current and developing trials that integrate both clinical and translational endpoints have the potential to transform management strategies in women with limited MBC.

The use of novel surgical and radiotherapeutic techniques for the treatment of few breast cancer metastases has been gaining considerable interest.[1,2] For both patients and physicians, the treatment of limited metastases, rendering a patient without evidence of cancer and, potentially cured, is an exciting concept. However, despite single-institution studies demonstrating improved outcomes compared with historic series of patients treated with systemic therapy alone, there is a lack of evidence proving that this treatment approach will extend progression-free survival (PFS) or overall survival (OS) for some patients with breast cancer with limited metastatic disease. Herein, we will review the evidence supporting the treatment of patients with oligometastatic breast cancer with ablative (surgery or radiation techniques). We will review what has been described for selection of these patients and their follow-up. We will also comment on ongoing clinical trials that may help to elucidate some of these questions. Finally, we will review what little is known about the biology driving the oligometastatic state.

Breast cancer has long served as a model to understand the mechanisms underlying the biology of metastatic cancer. Based on clinical observations in the late 19th and early 20th century, Halstead described an orderly and direct spread of malignancy from the primary tumor to regional lymph nodes and then to directly connected metastases.[3] The increase in radical and ultra-radical en-bloc operations resulted from this philosophy, attempting to remove all evidence of cancer. The continued evidence of distant cancer dissemination despite aggressive sur-

geries suggested a need for alternative hypotheses. The systemic hypothesis of metastasis was first described by Keynes and perhaps articulated most clearly by Fisher.[4] It suggested that widespread dissemination of disease occurred before clinical detection of the primary tumor. Therefore, cancers were dichotomized into either those that were localized to the primary site or those that were widespread. If widespread, increasing aggressive surgeries to the primary tumor and regional lymphatics, would not improve patient outcomes. Rather, systemic therapies delivered adjuvantly or neoadjuvantly could reduce distant metastases and, ultimately, have been integrated into standard treatment regimens. However, based on the clinical observations that not all breast cancers were widely metastatic at initial presentation, and that some patients with metastases had long disease-free intervals after metastasectomy and without systemic therapy, an alternative hypothesis was called for.

Hellman advanced our understanding of the natural history of metastasis by elucidating the spectrum hypothesis[5] in which some breast cancers remain locoregionally confined, others metastatic at presentation, and the remaining subset progressing from locoregional confinement to widespread metastases. Soon thereafter, Hellman and Weichselbaum described the clinically meaningful oligometastatic state, arising as a corollary of the spectrum hypothesis, where metastases limited in number and destination organ are unlikely to progress rapidly.[6] This was based on successful surgical removal of metastases, reported by Weinlechner as early as 1882,[7] and long-term survival (1939) and cure (1947) after metastasectomy.[8] Whether arising de

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novo at the time of diagnosis, or induced because of the effects of systemic therapy, patients with limited metastases present a potential opportunity to affect the natural history of MBC. In these patients, long-term disease control may be achieved with ablation of all known metastases. Identification of patients who could achieve long-term disease-free intervals after metastasis-directed therapy has the potential to shift treatment paradigms, in a similar way to curative intent treatment of women with breast cancer supraclavicular metastases.

It is not surprising that during the course of a century, different mechanisms underlying metastatic disease have been proposed. The disease that Hallstead saw on a regular basis, clinically detected locoregionally advanced breast masses, is now an uncommon presentation. More often than not, because of extensive education and screening efforts, patients present with relatively small breast cancers, often nonpalpable, with no adenopathy or involvement of lymph nodes and microscopic cells detected only with the aid of immunohistochemistry. Biologically, locoregionally advanced breast cancers and screen-detected breast cancers are different diseases. As the primary disease has changed, so might the behavior of the resulting metastatic disease. Similarly, with advanced imaging techniques such as high-resolution whole-body CT with or without PET and/or MRI, our ability to detect metastases is far greater than when investigations were limited to radiographic imaging at the time of clinically substantial symptoms. Just as we have developed different techniques to treat locoregional disease, so must we consider adapting the strategies that have been historically used for the treatment of metastatic disease.

INCIDENCE OF OLIGOMETASTASIS IN BREAST CANCER

Perhaps the first question that needs to be addressed is "how common are oligometastases in patients with breast cancer?"

KEY POINTS

- Oligometastases are a common presentation in many cancer types and are frequently represented in patients with breast cancer who are enrolled in clinical trials.
- Patients with oligometastases have a favorable prognosis compared to patients with more widespread metastases.
- Surgical complete resection of breast cancer metastases to the lung and liver in patients with oligometastases and long disease-free intervals have been associated with favorable survival compared with historical controls. Recent improvements in radiotherapy planning and delivery have allowed for the precise targeting of breast cancer metastases to any organ in the body with tumor control approaching that of surgical series.
- Data supporting use of surgery and/or ablative radiation are limited and primarily retrospective.
- Enrollment into ongoing prospective controlled studies is critical to determine if there is truly a benefit to either ablative radiation or surgical resection of all known metastases.

The true answer is that we do not know. The reason is that, up until recently, a diagnosis of metastatic disease was considered a dichotomous terminal event, with the number of metastases not considered to influence the eventual outcome or immediate treatment. Therefore, few studies have prospectively collected and reported the number of metastases at time of enrollment or metastatic diagnosis. More often, secondary analyses of prospectively (or retrospectively) collected data have sufficed to give us a hint at how often patients present with limited metastatic cancer.

From the available data, it appears that many, if not the majority of patients with MBC present with limited metastatic disease. Data from recently published first-line MBC trials, suggest that a large proportion of patients present with oligometastases, and those with fewer metastases have improved outcomes, as summarized in Table 1. Approximately 50% of patients enrolled in recent first-line MBC trials with differing estrogen receptor (ER) and HER2 status had less than two metastatic sites, and as many as 75% of patients with first-line MBC had less than four metastatic sites. The challenge of using these data is the definition of metastatic sites can be variable and may be interpreted by some to refer to individual metastases, individual organs, or organ systems (skeletal system). Despite this limitation, the data suggest that metastases are likely limited at presentation and not widespread, at least in patients who are considered candidates for prospective clinical trials. This is supported by analyses of large carefully followed breast cancer cohorts, where 17% of patients with early-stage breast cancer who progressed to metastatic disease presented with one to five metastases.[9] Interestingly, those who presented symptomatically with metastases were less likely to have oligometastases compared with those that were screen detected (14.5% vs. 26.7%; p = 0.22). These data are consistent with what has been described for other commonly occurring cancers, such as colorectal, prostate, and non-small cell lung cancer, which is reassuring if one assumes that there is some common underlying biology governing metastases.

WHAT IS THE BEHAVIOR OF PATIENTS WITH LIMITED METASTATIC DISEASE?

For the routine use of ablative therapies for patients with breast cancer with limited metastatic disease to be clinically meaningful, the rate of disease progression must be different in these patients than that of more widespread rapidly progressing cancer. Certainly, if the few detected metastases were the sentinels of an impending rapid spread of to come, then ablative therapy could not be a meaningful component of breast cancer management. What data that exist are limited and are often the same studies that describe the incidence of limited metastases. Therefore, to date, the level of evidence is not rigorous. However, the evidence that exists suggests that those who present with fewer metastases have a more protracted clinical course than those who present with more widespread metastases. Therefore, not all patients with lim-

TABLE 1. Frequency of Patients Enrolled in First-Line Metastatic Breast Cancer Trials with Limited Number of Metastatic Sites Who Appear Potentially Eligible for Ablative Therapy

Author/Study	Phase	No. of Patients	ER/PR+ (%)	HER2 Status	≤ 2 Met Sites (%)	≤ 4 Met Sites (%)	Arms	PFS (Months)
Albain 2008	II	599	32	-	57	91	1. Gem/Paclitaxel	9.89
							2. Paclitaxel	8.4
Bergh 2012	III	593	72	Pos	52	-	1. Sunitinib/Docetaxel	8.6
							2. Docetaxel	8.3
Tawfik 2013	II	30	77	Neg	50	-	1. Vinorelbine/Capecitabine	8.6*
Hurvitz 2013	IIR	137	54	Pos	49.3	-	1. Trastuz/Docetaxel	9.2
							2. T-DM1	14.2
Gianni 2013 AVEREL	III	424	51	Pos	50	-	1. Docetaxel/Trastuz	13.7
							2. Docetaxel/Trastuz/Bev	16.5
Sledge 2003 E1193	III	739	45	-	49	-	1. Doxorubicin	6*
							2. Paclitaxel	6.3*
							3. Doxorubicin/Paclitaxel	8.2*

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; met, metastases; PFS, progression-free survival; gem, gemcitabine; pos, positive; neg, negative; trastuz, trastuzumab; Bev, bevacizumab.
*Time to failure.

ited metastases should be considered to be showing the tip of the iceberg of their disease.

It is, therefore, instructive that in a large group of women treated with anthracycline-based systemic therapy, those with one to five metastases (number of metastases not metastatic organs) had significantly improved survival outcomes compared with those with more metastases.[10] Specifically, the median survival for women with five or more metastases was 146 weeks compared with 96 weeks in those with six to 12 metastases, compared with 80 weeks in those with 13 to 20 metastases (p < 0.01). Interestingly, a long-term analysis of patients with stage I to stage III breast cancer followed after initial locoregional therapy, found no difference in the time of presentation of metastases between those who presented with one to five metastases and those with more widespread disease, both being about 29.9 months. However, patients with one to five metastases had significantly longer OS after progression than patients with more widespread disease (median survival of 107.7 vs. 22 months; p = 0.001). Furthermore, the 5-year actuarial survival for patients with limited metastatic disease was 59.6% compared with 11.6% for those patients with widespread metastases.[9] These limited data suggest that an oligometastatic population of patients with breast cancer exists, these patients are well represented in the populations of recent clinical trials, and have a unique biology with longer survival than patients with more widespread metastases. However, these data are usually limited to single-institutional series, and it is clear that more robust analyses are needed in larger datasets.

THE EVOLUTION OF TREATMENT
Long-Term Disease Control with Systemic Therapies Alone

Currently, the standard of care (SOC) for MBC, similar to many other cancers, is delivery of systemic agents in the form of cytotoxics, biologics, and/or hormonal therapies, when appropriate, with radiation and/or surgery reserved for the management of symptomatic, nonresponsive, or potentially catastrophic metastases. However, chemotherapy is curative in a remarkably small number or patients with MBC. An analysis of more than 1,500 women with MBC treated with doxorubicin and alkylating agent-based chemotherapy reported only 1.9% remained in complete remission and free of relapse at 15 years.[11] These women were more likely to be younger, have a good performance status, be premenopausal, and have fewer metastatic sites. Furthermore, of the 1.9% (30 patients) of women who were disease-free after chemotherapy, one-third had metastasis-directed therapy in the form of tumor debulking or adjuvant therapy including hepatic artery infusion, radiation, or surgery. Similar studies have confirmed the rarity and existence of long-term control of MBC when treated with systemic therapies alone.[12,13]

For selected patients with limited metastatic disease from multiple histologies, elimination of all clinically detected metastases in addition to standard systemic therapies, either surgically or via ablative radiotherapy, has been shown to result in long-term disease control with greater percentages of patients without evidence of disease compared with those treated with systemic therapy alone. Resection or radiation of pulmonary,[14,15] hepatic,[16,17] central nervous system,[18,19] adrenal,[20,21] and multiple organ metastases[22-24] has been associated with 20% to 25% long-term disease control in these selected patients.

SURGICAL REMOVAL OF PULMONARY AND HEPATIC BREAST CANCER METASTASES

When these data are restricted specifically to patients with MBC, surgical resection of liver metastases has been shown to result in promising median PFS (14 to 34 months) and OS (24 to 63 months), whereas, after removal of pulmonary metastases, median survivals have ranged between 32 and 97

months, and 5-year survivals have ranged from 27% to 80%.[2,25] To date, all of the reported studies have been retrospective, and, therefore, although hypothesis generating, they are not conclusive of the benefits of these therapies. In one of the largest retrospective analyses of patients with breast cancer undergoing pulmonary metastasectomy pooling data from more than 460 women from multiple international institutions with specialty in pulmonary resection for metastases, approximately 60% of the patients had a single pulmonary metastasis and approximately 10% had three or more metastases. The median survival for this cohort was 35 months. The cumulative 5-year survival rate was 35%, the 10-year survival rate was 20%, and the 15-year survival rate was 18%. Patients with longer disease-free intervals, complete resections, and fewer metastases had improved OS. In women with a single metastasis completely resected and a disease-free interval longer than 36 months, the 5-year OS was 50% compared with 13% in those with multiple metastases and a disease-free interval less than 36 months.[25]

Similar results are seen in large retrospective analyses of patients with MBC undergoing hepatic metastasectomy; although, in general, the number of patients reported in these series are smaller than those reported for pulmonary metastasectomy. In one of the largest series of 86 patients, with primarily solitary (62%) and small (85% less than 5 cm) metastases with a median follow-up of 62 months, the median OS was 57 months.[26] Although the complication rate was 21%, most (72%) required no intervention, and there were no postoperative deaths. Ninety percent were able to undergo complete resection (R0) and only one patient had macroscopically positive resection margins (R2). Patients with a partial response (PR) to chemotherapy before hepatic resection had a median survival of 79.4 months compared with 22.9 months in those progressing before hepatic surgery (p < 0.001). Additionally, patients with ER/progesterone receptor (PR)-positive primary tumors had a median survival of 76.8 months after hepatic resection compared with 28.3 months in ER/PR-negative primary tumors (p < 0.001). Similar to those undergoing a pulmonary metastasectomy, a longer disease-free interval, longer than 24 months, was associated with longer OS (100.7 vs. 47.5 months; p < 0.001).

The importance of surgical removal or radiotherapy to all radiographically or metabolically detected metastases is becoming ever more important as systemic therapies are increasingly effective. Although systemic therapies have improved control of subclinical breast cancer metastases and prolonged of progression-free intervals in patients with MBC,[27] most long-term survivors following systemic therapy had aggressive treatment to all known metastases.[11] This is likely because of the fact that in patients with oligometastatic disease, from breast[28,29] as well as other primary tumors,[30] sites of progression are most likely in known metastases, and not in new metastatic locations. Therefore, ablative therapy to all known metastases has the potential to maximize the therapeutic benefit for these patients.

The importance of achieving an R0, complete resection in patients undergoing metastasectomy is clear from both pulmonary and hepatic metastasectomy data. From the largest analysis of patients undergoing pulmonary metastasectomy, those undergoing a complete resection had 5-year survival of 38%, 10-year survival of 22% and 15-year survival of 20%, and a median survival of 37 months compared with a 5-year survival of 18% and a median survival of 25 months in those who underwent incomplete resection (p = 0.0009).[25] Additionally, in patients undergoing a hepatic metastasectomy, those undergoing a complete resection had a median OS of 57 months compared with 33.6 months in patients undergoing R1/R2 resections (p = 0.17).

From these data clinical characteristics of preferred patients for surgical resection begin to emerge. Patients selected for surgery should have longer disease-free intervals. The exact disease-free interval is not known, but for both patients undergoing both pulmonary and hepatic resection has been reported at longer than 2 years.[26] Patients should also be able to undergo a complete resection, have fewer metastases, and have ER/PR or HER2-positive tumors.[2]

RADIOTHERAPY FOR BREAST CANCER METASTASES

Advances in the planning, targeting, and delivery of radiotherapy have recently added a new tool against oligometastases. Many patients with MBC are not candidates for surgery because of medical comorbidity, personal preference to avoid surgery in the setting of metastasis, or invasion of metastases into unresectable organs. In these situations, radiotherapy is ideally suited for the treatment of limited metastases. Newer radiation techniques, commonly termed stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR), but perhaps most accurately described as hypofractionated image-guided radiotherapy (HIGRT), precisely deliver single or few radiation treatments at doses 2 to 10 times that of conventional radiation treatments.[31] Derived from intracranial stereotactic radiosurgery, these treatments deliver radiation doses wrapped tightly around targeted metastases, while sparing surrounding normal tissues. These higher radiation doses are thought to engage additional tumoricidal mechanisms beyond DNA damage, including endothelial-mediated[32,33] and immune-mediated.[34,35] Although doses of at least 54 Gy have been shown necessary when using three radiation doses to target tumors in the lung and liver,[36] other more protracted dosing schemes have been shown effective as well.[22] These techniques have been shown to be effective even when targeting larger metastases[37] with treated metastasis control ranging from 70% to 90%.[31]

Perhaps the best data for the treatment of MBC with ablative radiotherapy comes from the University of Rochester.[29] A pooled analysis of 40 women with limited breast cancer metastases treated on two sequential protocols using radiotherapy for limited metastatic disease reported promising outcomes. The median time to enrollment was 12 months after diagnosis of metastases and 56 months after initial breast cancer diagnosis, and 90% had been pretreated with systemic therapy. The 2-year and 4-year PFS was 44% and 38%, respectively. At 4 years, the treated metastasis control

per patient was 80%. Four-year actuarial OS was 59%, the median survival was not reached. Patients with a solitary metastasis had improved PFS and OS compared with those with more than one metastasis (p = 0.028). Additionally, those with bone-only metastases fared particularly well with seven out of eight without evidence of recurrence and alive at a median follow-up of 50 months. Those with stable or responding lesions fared better than those with progressing lesions (2-year PFS 13% vs. 53%, p = 0.026; 2-year OS 63% vs. 81%, p = 0.061).

Identifying patients with breast cancer who are most likely to benefit from metastasis-directed radiation therapy remains a substantial challenge. Currently, patients with oligometastatic disease are selected via easily assessed clinical criteria. Patients with intracranial metastases, synchronous oligometastases, male gender, and nonadenocarcinoma histology have been associated with worse outcomes for receiving ablative radiotherapy in general.[38] In patients with breast cancer receiving ablative radiotherapy, specifically, those with bone metastases, bone-only metastases, single metastases, and stable or responding metastases have improved outcomes.[29] Similar results have been seen in large data sets of patients undergoing radiation for limited metastatic disease. In particular, a pooled analysis of more than 200 patients showed that patients with breast cancer and those with bone metastases had improved survival.[39] However, these clinical criteria are imperfect surrogates for identifying those with the true underlying biology of oligometastases.

Although these advanced radiation techniques have been shown to be effective in targeting few metastases in limited organs,[15,16,23,40] the studies evaluating patients with multiple metastases have been small, and limited to a few institutions.[22,24,28] Therefore, data are scarce describing treatment and toxicity outcomes of patients with more than three or two close metastases. In particular, when targeted metastases are in close proximity, the target organ and surrounding normal tissues are exposed to higher integral radiation doses. When three to four metastases are targeted, the volume of low-dose radiation in the body can be substantial in both target and normal organs. In this situation, the potential toxic effects of radiation are not well characterized. The reported toxicities of ablative radiotherapy are increasingly reported in the literature, but they are limited.[23,41-44]

CLINICAL TRIALS OF ABLATIVE RADIOTHERAPY AND SURGERY FOR CURATIVE TREATMENT FOR PATIENTS WITH BREAST CANCER AND LIMITED METASTASIS

Although the reported radiation and surgical series have been primarily retrospective, taken together they suggest long-term survival after metastasis-directed therapy in patients with limited breast cancer metastases. The benefits these patients derive may come from delaying progression in known metastases, as well as preventing known metastases from seeding new metastases. Furthermore, ablative radiation has been shown to have an abscopal effect, which may

improve outcomes by inhibiting progression of untreated micrometastatic foci.[45,46]

It must be remembered when evaluating the data for ablative therapy for limited breast cancer, benefits must be weighed carefully against the risks. Typically, the patients considered for these interventions are highly selected with good performance status and limited burden of disease. Therefore, the numerically high rates of median and OS may be because of selection or indolent biology. Additionally, some have questioned if promising outcomes observed after surgery or radiation of all oligometastases may be because of the underlying biology and not necessarily the metastasis-directed therapy.[47] Furthermore, given that other promising therapies for MBC, such as stem cell transplant were not successful,[48] we owe it to our patients to prove this benefit. This is particularly important when considering the toxicity of treatment, which can only be evaluated in robust analyses. In addition to postoperative complications, SBRT has been associated with vertebral body fractures, hepatic dysfunction, respiratory failure, and bowel perforation.[23] These could greatly affect a patient's quality of life, for potentially no benefit. Additional considerations should be given to cost of treatment. More advanced radiotherapy techniques have a substantially higher cost than conventional radiotherapy.[49] However, despite this cost, these treatments may prevent future need for palliative-intent radiotherapy, and may delay the need for costly targeted pharmaceuticals. Only prospectively collected high-quality data will answer these questions reinforcing the need to accrue to open trials.

SBRT is being used increasingly as a technique to treat patients with limited MBC. An international survey of radiation oncologists found that 61% were using SBRT to treat patients with limited metastases. Furthermore, of those not currently offering this treatment, more than half were planning to start offering SBRT for limited metastases in the next 3 years.[49] Although there is increasing evidence that in selected patients administration of SBRT for oligometastatic disease appears beneficial and its use is becoming more common, this has not been proven in controlled studies. Therefore, the initiation of randomized trials to ultimately prove clinical benefit is essential. However, conducting these trials may be increasingly difficult because of SBRT becoming the de facto SOC[50] without Level I evidence. Hence, the initiation of systematic and randomized clinical trials is important not only because of the potential to change or keep the SOC, but also because of the timing. There is currently a streamlined randomized phase II trial (NRG BR002) to determine if the ablation of all known metastases in addition to SOC improves PFS in women with one to two breast cancer metastases. If a PFS signal is seen, this will roll directly into a phase III study to determine if ablation of all breast cancer metastases can improve OS. This study is critical to determine what benefits, if any, there are to treating women with limited MBC.

To improve the radiotherapy techniques used to treat patients with metastases in close proximity and those with three

or more metastases, there is also a phase I dose de-escalation study (NRG BR001: NCT02206334) being conducted in which patients with breast, lung, and prostate cancer with two metastases in close proximity (less than 5 cm) or those with three to four metastases will receive radiation to all known sites of disease. Each metastasis will be assigned to one of seven regions (neck and mediastinum, lung central, lung peripheral, spinal, osseous, abdominopelvic, and hepatic) based on the potential for normal tissue toxicity. Doses for each region were selected based on all available data and expert consensus. Doses will be de-escalated to each region should toxicity be seen. An alternative approach, currently used in the SABR COMET study (NCT01446744) is a dose-stratified method.[51] Careful analysis of adverse events combined will help to truly understand the tolerances of normal tissues to this type of ablative radiation.

Recent investigations have suggested potential biologic markers of the oligometastatic state. Analyses of resected pulmonary metastases, and the combination of primary and metastatic tumors have identified a microRNA signature that, when present, identifies patients whose disease is unlikely to progress rapidly or in a widespread manner. In particular, increased expression of microRNA 200c was found to be associated with a polymetastatic phenotype in vivo as well as in clinically selected patients with oligometastatic disease.[52] When restricted to patients with lung metastases only, microRNA signatures can classify patients as oligometastatic compared with polymetastatic, and also differentiate those patients with a low recurrence probability following surgical resection.[53] Further validation is needed in prospective series to validate this as a potential patient selection tool.

Currently, there are no validated biomarkers for response evaluation after ablative radiotherapy for patients with oligometastatic disease. PET scans utilizing fludeoxyglucose as an imaging biomarker have shown potential for response evaluation after ablative therapy. Only 10% of patients with a PR on first postradiotherapy PET, and 29% of those with a complete response progressed during follow-up.[54] Additionally, PET was able to detect responses in those with nonmeasureable lesions by standard RECIST, particularly useful in patients with breast cancer who often present with osseous-only metastases. Another potential biomarker to evaluate response to ablative therapy is via enumeration of circulating tumor cells (CTCs). Already established as a prognostic tool for patients with MBC as well as a predictive tool evaluating response to systemic therapy,[55] the presence of less than five CTCs per 7.5 mL whole blood at baseline may also serve as a way to identify those patients with truly oligometastatic disease from the cohort of patients with few clinically apparent metastases. Furthermore, the ability of surgery or ablative radiotherapy to reduce the number of CTCs to less than five may predict good responses to therapy. Furthermore, the eradication of previously detectable CTCs after metastasectomy or ablative radiation may indicate that the primary sources of CTCs were the known and treated metastases and not from the occult sites reseeding after ablative therapy preventing durable long-term control.

In conclusion, from available data many if not most patients with MBC present with a limited number of metastases, which portents improved outcomes. Ablation of imaging-detected metastases, with either surgery or radiation, has been associated with long disease-free intervals for patients with breast cancer. Although ablative therapies are gaining in popularity, only now are prospective trials open to identify the role of ablative therapy in oligometastatic breast cancer. Patients should be enrolled in these studies to identify the true effect of ablative therapy. Although early data are beginning to elucidate the biologic underpinnings of patients with oligometastatic disease, more work is needed, and biomarkers need to be validated in this patient population to better identify responses to treatment. All of this work is needed to truly determine if there is potentially a subset of patients with MBC that can achieve long-term survival. With better identification of which patients belong in this subset and what the utility is of the ablative therapy options, a new treatment paradigm may become the cure for a subset of patients with MBC.

Disclosures of Potential Conflicts of Interest

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BREAST CANCER

Controversies in Neoadjuvant Therapy for Breast Cancer: Surgery, Radiation, and Therapeutic Trials

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Neoadjuvant Therapy for Breast Cancer: Controversies in Clinical Trial Design and Standard of Care

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OVERVIEW

Neoadjuvant therapy for breast cancer has been increasingly used in recent years as first-line treatment for operable breast cancer—serving as both a management strategy and a research tool. In addition to the established clinical benefits of down-staging more locally advanced cancers and improving breast-conservation rates, investigators have recognized the potential advantages of this approach in developing new therapies. Preoperative systemic therapy provides the opportunity for in vivo assessment of pharmacodynamic markers to assess biologic effects and allows new compounds to be tested in a more responsive, treatment-naive population. In addition, early surrogates of response, such as pathologic complete response (pCR) and residual cancer burden, provide proximate measures that correlate with long-term outcomes, thus potentially shortening the time needed to identify effective adjuvant therapies. Despite the advantages of neoadjuvant therapy for research and clinical practice, its use is characterized by persistent controversy and healthy debate regarding how to optimally use research findings and when to integrate them into the standard of care for daily management. Among the controversies surrounding neoadjuvant therapy use are questions about defining the best endpoint for assessing treatment efficacy, deciding when results from research should be used in daily clinical practice, and how the growing use of neoadjuvant therapy affects locoregional treatments.

Neoadjuvant therapy for breast cancer has gained traction in recent years as both a management strategy and research tool. In addition to the established benefits of downstaging inoperable cancers and improving breast-conservation rates,[1,2] investigators have recognized this approach's potential advantages for developing new therapies. Preoperative therapy provides the opportunity for in vivo assessment of pharmacodynamics markers to assess biologic effects and allows new compounds to be tested in a more responsive, treatment-naive population. In addition, early surrogates of response, such as pCR and residual cancer burden, provide proximate measures that correlate with long-term outcomes, thus potentially shortening the time needed to identify effective adjuvant therapies. But with these advantages, come challenges, both in optimizing the research data that is obtained and integrating this approach into the standard of care. What are the appropriate endpoints for neoadjuvant clinical trials? When do we integrate findings from these clinical trials into standard systemic therapy approaches? And finally, what are the implications of neoadjuvant therapy and trials on locoregional surgical and radiation therapy outcomes and approaches? These controversies continue to evolve as our understanding of the biology and natural history of breast cancer subtypes and use of preoperative therapy grows.

APPROPRIATE ENDPOINTS FOR NEOADJUVANT CLINICAL TRIALS

There has been substantial enthusiasm for pCR as a surrogate marker in neoadjuvant trials. This arose out of observations in several randomized trials in which patients who experienced a pathologic response on the whole had lower rates of recurrence than those who did not—a prognostic benefit that was even greater when evaluated within breast cancer receptor subsets.[3,4] The subsequent U.S. Food and Drug Administration (FDA) meta-analysis defined the magnitude of the difference in event-free survival (EFS) for pCR compared with non-pCR prognostic groups as defined by the eradication of all invasive cancer in the breast and axillary lymph nodes.[5] This analysis showed that overall pCR rates and the magnitude of the differences in outcome were highest in the HR-negative/HER2-positive and triple-negative subsets.

But for pCR to be utilized as a surrogate marker in clinical trials of new therapies, it must also be a predictive marker. As such, one would hypothesize that an increase in pCR rate in a population of patients receiving investigational therapy would be associated with a subsequent improvement in event rates (EFS, overall survival [OS]) over patients in the control group. The FDA meta-analysis was not able to demonstrate such a relationship in the trials that were included in their analysis. The authors cautioned that this did not rule out the

possibility that such a relationship exists, but that, among the studies included in that analysis, no such association was seen. This could have been caused by the overall low rates of pCR in those studies and the fact that only one trial included targeted therapy. That trial was the NOAH trial,[6] which randomly selected patients to receive a preoperative anthracycline/taxane regimen with or without trastuzumab, and it showed that trastuzumab significantly improved pCR rates and subsequently improved EFS (hazard ratio [HR] 0.59, p = 0.013). This subsequently translated to a benefit of trastuzumab in the adjuvant setting that was demonstrated in the combined National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31/North Central Cancer Treatment Group (NCCTG) 9831 trials with an absolute improvement in disease-free survival (DFS) of 12% (HR 0.48, p < 0.0001).[7]

Although these studies appear to support pCR as a good surrogate predictive marker in HER2-positive disease, concerns were raised again when the results of the NeoALTTO and ALTTO trials were reported.[8-10] These trials investigated whether the receptor tyrosine kinase inhibitor, lapatinib, would further improve outcomes for patients treated with chemotherapy and trastuzumab in the neoadjuvant and adjuvant settings, respectively. Patients in the NeoALTTO trial were randomly assigned to 12 weeks of paclitaxel with either trastuzumab alone, lapatinib alone, or the combination. Patients then went to surgery and received anthracycline postoperatively. Patients receiving the combination of trastuzumab and lapatinib had a significantly higher pCR rate than those receiving trastuzumab alone (pCR rates 51.3 vs. 29.5, p = 0.0001). In light of the encouraging pCR findings, the large, adjuvant ALTTO trial was launched, while follow-up on NeoALTTO continued. The treatment plan in the ALTTO trial differed in an important respect from NeoALTTO: all chemotherapy was given preoperatively, includ-

ing anthracycline. Interestingly, the trials matured, and the results were published within months of each other. Notably, EFS, OS, and the association between pCR and EFS or OS (analyzed by landmark analysis at 30 weeks after random selection) were secondary endpoints in the NeoALTTO trial, with far less power to detect a significant difference than the ALTTO trial. Despite the significant improvement in pCR rate for the combination of trastuzumab and lapatinib over trastuzumab alone, EFS in the NeoALTTO trial did not differ between the combination and trastuzumab groups (EFS 0.78 and 0.47–1.28, respectively, p = 0.33). pCR retained its prognostic significance in landmark analyses showing that 3-year EFS and OS were significantly improved for women who achieved pCR compared with those who did not (p = 0.0003 and p = 0.005, respectively). Similarly, the adjuvant ALTTO trial also failed to show a benefit in DFS for patients receiving the combination of trastuzumab and lapatinib compared to those receiving trastuzumab alone. The HR was 0.84 (97.5% CI, 0.70 to 1.02) on the basis of about 2,100 patients in each of the two groups. The two-sided p value of 0.048 was not significant because the investigators had added another comparison: the noninferiority of trastuzumab followed by lapatinib versus trastuzumab, both for a total of 1 year.

In light of these results, should pCR be abandoned as a surrogate predictive marker in neoadjuvant trials? Limitations in the design of these trials would potentially lead to that conclusion erroneously; therefore, several issues must be taken into account. First, because the anthracycline component of the chemotherapy regimen was given postoperatively in the NeoALTTO trial, the comparison of pCR rates hinged only on the differences between the taxane and targeted therapies. This may have exaggerated the effects of lapatinib, since anthracyclines are well known to be active in HER2-positive disease,[11] and dampened the ability of pCR to predict survival endpoints in NeoALTTO when such a critical component of therapy was given postoperatively. Differences in the design of NeoALTTO and ALTTO also may have played a role in the inability of ALTTO to demonstrate a DFS benefit. Patients in ALTTO were more likely to have node-negative or estrogen receptor (ER)-positive disease than those in the NeoALTTO trial, thus providing a lower overall event rate. Moreover, the HR achieved in the ALTTO trial would have been predicted by the FDA meta-analysis, as shown by a subsequent statistical analysis.[12] The meta-analysis showed that the EFS HR for patients with HER2-positive breast cancer achieving a pCR compared with those not achieving a pCR was 0.39 (95% CI, 0.31 to 0.50), a 61% reduction in the hazard of recurrence. A 20% improvement in pCR rate with the combination of trastuzumab and lapatinib over trastuzumab alone, as seen in the NeoALTTO trial, would result in one in five patients moving from the no pCR Kaplan-Meier curve to the pCR curve. This would predict an HR for the comparison to fall to 0.83—very similar to the 0.84 seen in both the NeoALTTO and ALTTO trials.

Moving forward, pCR may still be the appropriate endpoint for neoadjuvant trials but with study design requirements that will make it possible to accurately assess pCR to

KEY POINTS

- Neoadjuvant systemic therapy improves surgical outcomes and is a platform for translational research and clinical trials.
- New therapeutic approaches that result from neoadjuvant trials ideally demonstrate benefits in terms of pathologic complete response and event-free and overall survival.
- Downstaging with neoadjuvant therapy enables more women to undergo breast conservation with lumpectomy and breast radiotherapy.
- Locoregional cancer outcomes comparable to mastectomy are expected from breast conservation in appropriately selected patients after neoadjuvant therapy.
- Postmastectomy radiotherapy appears to be of most benefit after neoadjuvant therapy in those with extensive clinical stage III breast cancer (T3–4, N2–3).
- The extent of locoregional therapy necessary for those who downstage to pathologically node negative after neoadjuvant therapy is evolving and clinical trials are ongoing.

select the most promising agents to take forward to confirmatory trials. First, all chemotherapy should be given before surgery. Second, pathologic assessment of residual diseae at surgery must use the FDA-recommended definition of elimination of all invasive cancer in the breast and axillary lymph nodes. Third, the neoadjuvant trial and subsequent adjuvant trial must have identical chemotherapy treatment plans and minimal differences in variability in postoperative treatments such as radiation. Finally, the subsequent confirmatory phase III trial should be sufficiently powered for the EFS HR that would be predicted by the improvement in pCR. The FDA has proposed such a strategy in its guidance allowing pCR to be considered an endpoint for accelerated approval of drugs before completion of confirmatory trials.[13]

INTEGRATING FINDINGS FROM NEOADJUVANT CLINICAL TRIALS INTO STANDARD SYSTEMIC THERAPY

The neoadjuvant setting is used to test both new agents on the path to regulatory approval and previously approved agents that could provide benefit in this setting. In addition to improving EFS, such trials may show other important clinical benefits of new neoadjuvant approaches for patients. These include improving the likelihood of resectability or breast conservation or reducing the need for full axillary dissection. These are tangible benefits to patients that are demonstrable at the time of initial report of pCR findings, and they do not require waiting for reductions in locoregional/distant recurrence or survival.

When should the practicing physician implement new neoadjuvant strategies with existing drugs for these outcomes? In this situation, toxicity plays a key role in determining whether the potential benefit is worth the risk for the individual patient. An example of this conundrum is whether to add carboplatin or bevacizumab to anthracycline/taxane-based neoadjuvant chemotherapy in patients with triple-negative (ER-/PR-/HER2-) breast cancer. pCR rates in triple-negative disease with standard therapy are typically in the 35% to 40% range, and patients without a pCR have an abysmal prognosis, with a median survival of 3 years.[5] Platinum analogs have been demonstrated to be highly active in BRCA-mutated breast cancer, a group that significantly overlaps with sporadic triple-negative disease. Several small neoadjuvant trials showed higher than expected pCR rates (> 70%) with the addition of carboplatin to anthracycline/taxane-based regimens in BRCA-mutation carriers. Thus, a phase II randomized trial, Cancer and Leukemia Group B 40603, was undertaken to evaluate this strategy in unselected patients with locally advanced, triple-negative disease.[14] This trial randomly selected 443 patients to receive weekly paclitaxel with or without concurrent carboplatin (every 3 weeks at area under the curve = 6), followed by four cycles of doxorubicin and cyclophosphamide. A 2 × 2 factorial design was employed to simultaneously evaluate the effect of adding bevacizumab to this treatment strategy. The addition of carboplatin to the standard chemotherapy regimen significantly

increased the pCR rate (breast and axilla) from 41% to 54% (p = 0.0029). Several additional proximate outcomes showed improvement as well, with carboplatin increasing the proportion of patients who converted from clinical node-positive to pathologically node-negative status and the proportion who became eligible for breast-conserving therapy.

But these benefits did come with a price. The overall number of serious adverse events, defined as any unexpected grade 3 or higher toxicity or toxicity that required hospitalization or surgical intervention, was higher in the carboplatin arm, including higher rates of febrile neutropenia and severe nausea, vomiting, and dehydration. Patients assigned to carboplatin were more likely to miss two or more doses of paclitaxel and required more dose reductions of paclitaxel, and 20% were unable to complete all planned doses of doxorubicin/cyclophosphamide. Thus, the risk/benefit equation of adding carboplatin to standard neoadjuvant chemotherapy for triple-negative breast cancer is complicated. In the absence of EFS/OS data, the most appropriate candidates are those who would benefit most from surgical downstaging; those with conditions that increase intolerance to standard therapy could have that therapy compromised with the addition of carboplatin. The treatment decision requires individualization of therapy and extensive discussion with the patient about possible implications before embarking on this new treatment approach.

IMPLICATIONS OF NEOADJUVANT THERAPY ON LOCOREGIONAL TREATMENT WITH RADIOTHERAPY

The increasing use of neoadjuvant systemic therapy for breast cancer has had the dual effect of providing important benefits and causing significant controversy regarding the locoregional treatment of breast cancer with radiotherapy. One of the clearly established benefits of neoadjuvant therapy is that it enables more women to undergo breast conservation with lumpectomy and breast radiotherapy who otherwise would have been treated with mastectomy.[1,2] Despite results demonstrating in-breast recurrence after breast conservation was similar for those who received neoadjuvant compared with adjuvant chemotherapy,[1] there was some reluctance expressed for breast-conservation approaches after neoadjuvant therapy for those women whose extent of disease before neoadjuvant therapy made them initial mastectomy candidates.[15] This was based on findings from the NSABP B-18 clinical trial that reported the in-breast recurrence rate was higher in patients who were initially mastectomy candidates and were converted to breast conservation by neoadjuvant therapy, compared with those who were initially candidates for breast-conserving surgery (15.7% vs. 9.9%, respectively; p = 0.04).[16] More recent studies have found that this local recurrence pattern is related to more aggressive biologic behavior of larger, higher stage and grade breast cancers in the group of women who are initially mastectomy candidates and not because they underwent breast conservation as a result of downstaging following neoadjuvant therapy.[17] A

growing body of literature now supports that when appropriately selected by downstaging, breast conservation can yield comparable locoregional cancer outcomes in comparison to mastectomy after neoadjuvant therapy irrespective of age, subtype, and whether mastectomy was initially intended.[17-20] As newer neoadjuvant agents are utilized resulting in even higher rates of pathologic response in some breast cancers,[5] women with more locally advanced breast cancer are even better poised to feasibly and safely achieve breast conservation when desired. In contrast, the increasing use of neoadjuvant systemic therapy has created considerable controversy and debate regarding the optimal use of postmastectomy radiotherapy in this setting.

INDICATIONS FOR POSTMASTECTOMY RADIOTHERAPY WHEN NEOADJUVANT SYSTEMIC THERAPY IS DELIVERED

Clinical decision making regarding the use of postmastectomy radiotherapy has been established from numerous randomized clinical trials and meta-analyses where pathologic staging from mastectomy as the first line of breast cancer therapy was the determinant of receiving radiotherapy.[21,22] This data consistently demonstrates that for women with axillary node-positive breast cancer, the addition of chest wall and regional nodal radiotherapy after mastectomy and adjuvant chemotherapy can improve breast cancer survival by a few percent, in addition to providing large gains in locoregional cancer control.[21,22] This benefit in survival from postmastectomy radiotherapy is similarly seen for those patients with four or more involved axillary nodes, as well as many with one to three positive axillary nodes.[22] As a result, it is generally recommended that patients who have axillary nodal metastases receive radiotherapy to the chest wall and regional nodes after mastectomy, and conversely, radiotherapy is not typically recommended after mastectomy when negative axillary nodes are found. The absence of similar evidence when neoadjuvant chemotherapy is delivered as first line of breast cancer treatment has led to conflicting opinions regarding which factors are most important for determining postmastectomy radiotherapy benefit: the clinical stage before neoadjuvant chemotherapy or the pathologic stage at surgery after neoadjuvant chemotherapy. It is clear that both sides of the debate regarding postmastectomy radiotherapy use in the setting of neoadjuvant chemotherapy stems from a desire to minimize harm to patients with breast cancer. Those who endorse that postmastectomy radiotherapy should be recommended based on the presence of positive axillary nodal metastases before neoadjuvant therapy caution that omitting radiotherapy based on chemotherapy response places women at risk for worse breast cancer mortality.[23] On the other hand, some support the idea that pathologic node status after neoadjuvant chemotherapy is the important factor, and they argue that for patients who are downstaged to pathologically node-negative status, postmastectomy radiotherapy may not offer significant benefit and therefore adds excess toxicity.[24]

Most of the literature on the use of postmastectomy radiotherapy after neoadjuvant chemotherapy is from retrospective case studies from single institutions (Table 1). The largest single series that retrospectively examined outcomes after neoadjuvant chemotherapy by postmastectomy practice patterns is by Huang et al, in 676 women treated between 1974 and 2000 on six prospective clinical trials studying anthracycline based neoadjuvant chemotherapy at The University of Texas MD Anderson Cancer Center.[25] Roughly 80% (542) received radiotherapy, while approximately 20% (134) were observed postmastectomy. The majority of cases were clinical stage III (70%), and only 8% and 14%, respectively, experienced a pCR from neoadjuvant therapy in the observed and irradiated groups. The 10-year rate of locoregional recurrence (LRR) was significantly lower (p = 0.0001) and OS was better (p = 0.006) in the group that received postmastectomy radiotherapy (Table 1).[25] In a multivariate Cox regression analysis of factors associated with LRR, radiation use was the most significant variable, with an HR for no radiation of 4.7 (95% CI, 2.7 to 8.1; p < 0.0001). Other factors found to be important for developing LRR included 20% or more pathologically positive axillary nodes after neoadjuvant therapy and clinical stage IIIB to stage IV disease. A subsequent study from this institution reported cancer out-

TABLE 1. Retrospective Studies Evaluating Cancer Outcomes in Relationship to Postmastectomy Radiotherapy Use after Neoadjuvant Chemotherapy

Author/ Treatment Era	No. of Patients	Follow-up (Months)	Path Response	Clinical Stage	PMRT Yes/No	LRR %	OS %
Huang[23] 1974–2000	676	RT, 73 No RT, 66	RT, 14% No RT, 8%	II, 30% III, 70%	Yes No	11* 22	54* 47
McGuire[24] 1982–2002	106	62	100% pCR	II, 30% III, 70%	Yes No	5 10	- -
LeScodan[25] 1990–2004	134	91	100% ypN0	II, 63% III, 37%	Yes No	4 12	88 94
Shim[26] 1998–2009	151	57	100% ypN0	II, 60% III, 40%	Yes No	2 8	93 90

Abbreviations: PMRT, postmastectomy radiotherapy; LRR, locoregional recurrence; OS, overall survival; RT, radiotherapy; ypN0, pathologically node-negative.
*Significant statistical difference in comparison with no PMRT.

comes relative to pattern of postmastectomy radiotherapy use in 106 women who experienced pCR from neoadjuvant chemotherapy.[26] The majority of cases were clinical stage III (70%). When the entire group was analyzed, there was no significant advantage in LRR in the 72 patients who were irradiated compared with those who received observed postmastectomy (p = 0.40; Table 1). However, when only the 74 patients with clinical stage III disease were analyzed, postmastectomy radiotherapy was associated with a significantly lower 10-year rate of LRR (7.3% in the patients who were irradiated vs. 33.3% in those who did not receive radiotherapy postmastectomy; p = 0.040) and better OS (77.3% for the patients who were irradiated and 33.3% for the patients who were not irradiated, p = 0.0016), leading the authors to recommend routine treatment for patients with clinical stage III disease, even when achieving a pCR.[26] Two other studies examined cancer outcomes retrospectively by postmastectomy use in those who were downstaged to pathologically node-negative (ypN0) following neoadjuvant chemotherapy. Le Scodan et al reviewed 1,054 patients with breast cancer treated with neoadjuvant chemotherapy at Institut Curie and René Huguenin Hospitals between 1990 and 2004 to find 134 that had ypN0 status after neoadjuvant chemotherapy and mastectomy.[27] Of the 134 eligible patients, 78 (58.2%) received postmastectomy radiotherapy and 56 (41.8%) did not. At a median follow-up time of 91.4 months, the 5-year LRR-free survival and OS rate was 96.2% and 88.3% with postmastectomy radiotherapy and 92.5% and 94.3% without postmastectomy radiotherapy, respectively (p = not significant), and no significant changes in cancer outcomes were found at 10 years. Another retrospective study conducted in nine Korean institutions, identified 417 patients with clinical stage II-III breast cancer who achieved a ypN0 at surgery after receiving neoadjuvant chemotherapy between 1998 and 2009. Of these, 151 patients underwent mastectomy, and 105 (69.5%) received postmastectomy radiotherapy. There was no significant benefit in reducing LRR or improving OS in the radiotherapy group (Table 1).[28] From these studies, it can be observed that postmastectomy radiotherapy appears to be of most benefit after neoadjuvant therapy in those with extensive clinical stage III disease (T3– 4, N2–3), even when a pCR is observed and when axillary nodes remain pathologically involved.

PATHOLOGIC RESPONSE TO NEOADJUVANT THERAPY AS A PREDICTOR OF LRR RISK AND NEED FOR POSTMASTECTOMY RADIOTHERAPY

Evidence supports that neoadjuvant chemotherapy response is linked to lower rates of subsequent LRR risk in the absence of postmastectomy radiotherapy. Mamounas et al[29] analyzed LRR rates in approximately 3,000 women enrolled onto two NSABP clinical trials evaluating neoadjuvant chemotherapy (NSABP B-18 and NSABP B-27). Both protocols specified that patients treated with mastectomy were not allowed to receive any radiotherapy. The combined analysis of these two trials provides important insight on the rates, patterns, and

independent predictors of LRR after neoadjuvant chemotherapy and mastectomy. The 10-year cumulative incidence of LRR was 12.3% for patients who underwent mastectomy (local, 8.9%; regional, 3.4%). Independent predictors of LRR postmastectomy, were clinical tumor size, clinical node status, and pathologic node status/pathologic breast response. In particular, those with clinically involved nodes before chemotherapy who had pathologically node-negative disease (ypN0) at surgery (with or without pCR in the breast) had a lower LRR than those who were found to have persistent nodal metastases pathologically. In a small subset of 102 patients undergoing mastectomy with clinically positive nodes before neoadjuvant chemotherapy who were downstaged to ypN0 afterwards, the risk of chest wall and regional nodal recurrence was between 0% and 10.8% at 10 years. These LRR rates fit into a low-risk category of patients who may not experience a significant benefit from postmastectomy radiotherapy, particularly in terms of improved survival, and could be spared the associated toxicity. It is important to emphasize that the results of the combined analysis of NSABP B-18 and B-27 are primarily applicable to patients with clinical stage I to II disease; 55% of the patients presented with cT1–2N0 disease, 20% with cT1–2N1 disease, and 6% with cT3N0 disease. Only 9% of the patients presented with cT3N1 disease.

The combined analysis of NSABP B-18 and B-27 supports that for patients who have positive nodes before neoadjuvant chemotherapy, the rate of LRR can be modified downward if the nodes become pathologically node-negative after neoadjuvant chemotherapy (particularly if there is also pCR in the breast). These findings are supported by the outcomes reported in the retrospective studies in those downstaged to ypN0 after neoadjuvant therapy as described above.[27,28] However, prospective data are needed to ensure omission of postmastectomy is safe given the extensive data supporting its benefit in improving survival for the treatment of node-positive breast cancer.[21,22] The NSABP B-51/Radiation Therapy Oncology Group (RTOG) 1304 phase III clinical trial (NCT01872975)[30] is designed to answer whether regional radiotherapy improves the invasive breast cancer recurrence-free interval rate (local, regional, and distant recurrences and deaths resulting from breast cancer) in women who present with clinical N1 axillary node disease (documented pathologically by needle biopsy) before neoadjuvant chemotherapy and then become pathologically node-negative at time of surgery. After mastectomy, patients are randomly assigned to no radiotherapy or chest wall and regional nodal radiotherapy, and after lumpectomy, random assignment is to breast radiotherapy alone or breast and regional lymph node radiotherapy.

CONCLUSION

In summary, the neoadjuvant setting provides a wealth of opportunities to identify better treatment strategies through clinical trials, evaluate new drugs for efficacy, and improve locoregional outcomes for individual patients. However, to fully realize these opportunities, clinical trials must be de-

signed with appropriate endpoints, sample size, and patient populations. pCR may be a proximate surrogate endpoint that can speed the process of identifying promising new therapies, but its ability to accurately predict meaningful, long-term outcomes has not yet been established. More work is necessary to determine the magnitude of increase in pCR within specific breast cancer populations that will lead to im-

provement in EFS, so that only the most promising agents move forward to confirmatory trials. In the interim, increases in pCR may lead to accelerated approval of new drugs or new therapeutic strategies with existing agents that can benefit patients. But these proximate benefits must be weighed against toxicity and treatment effect of these agents that could potentially undermine later outcomes.

Disclosures of Potential Conflicts of Interest

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BREAST CANCER

Individualizing the Approach to the Older Woman with Breast Cancer

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Management of Older Women with Early-Stage Breast Cancer

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OVERVIEW

Breast cancer is a disease of aging. The average age at diagnosis is 61, and the majority of deaths occur after age 65. Caring for older women with breast cancer is a major challenge, as many have coexisting illness that can preclude optimal breast cancer treatment and which frequently have greater effect than the breast cancer itself. Older patients with cancer should be screened or have a brief geriatric assessment to detect potentially remediable problems not usually assessed by oncologists (e.g., self-care, falls, social support, nutrition). Older women with early-stage breast cancer should be treated initially with surgery unless they have an exceedingly short life expectancy. Primary endocrine therapy should be considered for patients who have hormone receptor–positive tumors and a very short life expectancy, an acute illness that delays surgery, or tumors that need to be downstaged to be resectable. Sentinel node biopsy should be considered for patients in whom it might affect treatment decisions. Breast irradiation after breast-conserving surgery may be omitted for selected older women, especially for those with hormone receptor–positive early-stage breast cancer that are compliant with adjuvant endocrine therapy. The majority of older women with stage I and II breast cancer have hormone receptor–positive, HER2-negative tumors, and endocrine therapy provides them with optimal systemic treatment. If these patients have life expectancies exceeding at least 5 years, they should be considered for genetic assays to determine the potential value of chemotherapy. Partnering care with geriatricians or primary care physicians trained in geriatrics should be considered for all vulnerable and frail older patients.

Breast cancer is a disease of aging. Currently, the average age at onset of diagnosis in the United States is 61—similar to other developed nations—and the majority of deaths occur in women age 65 and older. The challenges of caring for these patients will continue to increase as the numbers of older women surge in our aging population. Despite the large numbers of older patients with breast cancer, little clinical trial data exist to guide decision making. This is of concern since many older patients with breast cancer have comorbidities that result in loss of function that may compromise their breast cancer care. Of note, and perhaps somewhat because of these limitations, breast cancer–specific survival when adjusted for age is less for older patients, suggesting that these patients are not being given optimal state-of-the-art care.[1] This article addresses issues related to surgery, radiation therapy, and adjuvant therapy for older women with early-stage breast cancer. Outstanding references related to these issues are available.[2-4]

SURGICAL MANAGEMENT

In the 1980s, the question regarding surgery in older patients was, "Can we?" Herbman et al showed that older women could tolerate mastectomy and had a substantial long-term survival and concluded the standard treatment—mastec-

tomy at that time—should not be withheld from these patients.[5] Today the question is different: "Should we?" In many ways, early-stage breast cancer in older, healthy women should be considered more of an inconvenience than a threat to their lives. The treatment should minimize not only the inconvenience but also the morbidity produced. Although radiation to the breast is well tolerated, it does increase breast pain, fibrosis, and retraction for at least a limited amount of time, as shown in Cancer and Leukemia Group B (CALGB) 9343.[6] In many older women with comorbidities, the effect of breast cancer on their quality of life is less than in younger patients because of their limited life expectancy. In these older women especially, the major goal should be limiting treatment to the minimum amount necessary to prevent locoregional recurrence during the patient's remaining lifetime.

When the older woman presents with early-stage breast cancer, the surgeon must evaluate the size and location of the cancer by physical exam and imaging and then determine the patient's general health status and life expectancy. For those with severe comorbidities and limited life expectancy, it may be best to avoid surgery all together. If the cancer is hormone-receptor positive, the use of an aromatase inhibitor (AI) or tamoxifen can often control the cancer for the duration of the patient's life.[7] For healthier older women, the decision is be-

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tween lumpectomy and mastectomy and between sentinel node biopsy, axillary dissection, or no axillary surgery.

If the surgeon's assessment suggests that lumpectomy is likely to be successful, this is almost always the best approach, as it limits surgical morbidity and likely provides the best quality of life. In many cases, this is the only surgery required and radiation may not be needed. If lumpectomy does not initially appear possible, and the patient's disease is hormone receptor positive, the surgeon must decide if preoperative hormone therapy could potentially convert the patient to conservation.[8] If so, this should be offered to the patient, setting the expectation that it may be 6 months or longer before surgery is undertaken. For those who do not have hormone receptor–positive disease or who will not be able to be converted to conservation, immediate mastectomy is appropriate. For these patients, reconstruction should be considered, being mindful of their underlying health. Older women should not be excluded from having reconstruction, and it should not be assumed that all older women want reconstruction. Reconstruction is very much an individual decision based on the patient's health, lifestyle, and expectations.

The next issue is axillary surgery, a decision that should be based on whether the patient has clinically node-positive or node-negative disease. For those older women with clinically positive axillary nodes who are surgical candidates, axillary dissection is appropriate. Axillary radiation instead of dissection can be considered for those felt not to be surgical candidates. For those who have clinically node-negative disease and who require mastectomy, sentinel node biopsy is appropriate with conversion to axillary dissection if node positive. Older women with low volume axillary disease can likely avoid postmastectomy radiation; hence, dissection may often be the least morbid and most convenient management approach. For those undergoing lumpectomy, sentinel node biopsy is often not needed. It has been shown that for clinical stage I hormone receptor–positive cancers in patients who do not undergo any axillary surgery and do not have radiation, only 3% recur in the axilla at 10 years.[9] For those radiated, almost none will recur in the axilla. For women who

have hormone receptor–negative disease or larger tumors or for whom the decision regarding chemotherapy will be determined by the node status, sentinel node biopsy is appropriate, in accordance with the Z11 trial[10,11] and AMAROS trial findings.[12] Otherwise, sentinel node biopsy can be avoided.

Much hinges on what we consider to be an acceptable level of locoregional recurrence. A current recommendation is that an acceptable locoregional recurrence rate should be 1% or less per year or within 10% at 10 years.[13] This is in line with our acceptance of local recurrence for lumpectomy plus radiation in women younger than age 50, for whom the in-breast recurrence rate at 10 years is approximately 10%.[14] If this rate is acceptable, then lumpectomy without radiation—with an approximately 9% risk of in-breast recurrence at 10 years—for clinically stage I, hormone receptor–positive breast cancer should be acceptable.[6]

In summary, surgery in the older patients should be the minimum necessary to keep the risk of locoregional recurrence to an acceptable level and within the life expectancy of the patient. In many women with early-stage breast cancer, lumpectomy plus hormone therapy is all that is needed.

RADIATION THERAPY

After lumpectomy, the decision to add radiation therapy for older women needs to be carefully considered. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) published an updated analysis using individual patient data from 10,801 patients included in 17 randomized trials of radiation after breast-conserving surgery.[15] This publication revealed that the addition of radiation therapy was associated with a highly significant absolute benefit of 15.7% in any first recurrence (local, regional, or distant recurrence) at 10 years ($2p < 0.00001$). The benefits of radiation therapy varied when adjusted for estrogen receptor status, grade, and age.

The potential benefits of radiation among age groups in the EBCTCG analysis revealed that the absolute benefit of radiation therapy depended on the baseline risk of recurrence: a function of age. With increasing age, the baseline risk of recurrence was lower, leading to a smaller but still significant absolute benefit of radiation overall. In women older than age 70, the baseline risk of recurrence and therefore the benefit derived from radiation was about half—an 8.9% absolute reduction in a 10-year risk of a locoregional or distant recurrence. This analysis was based on chronologic age and included healthy older women as well as those with comorbidities.

This concept of proportional benefits—that the absolute benefit of radiation therapy varies with the underlying risk of recurrence—raises the question of whether radiation therapy following breast-conserving surgery can be safely omitted if the absolute risk is low. This question was directly addressed by four randomized trials of endocrine therapy with radiation therapy or endocrine therapy alone in older women with estrogen receptor–positive breast cancer (Table 1). Each of these trials showed that the addition of radiation therapy to

KEY POINTS

- The goals of treatment of older patients are typically different than for younger patients and should be clearly defined when making treatment recommendations.
- Life expectancy and comorbidities are key factors in treatment decisions.
- Surgical and radiation oncology decisions should focus on optimizing local control while minimizing a negative effect on quality of life.
- Adjuvant chemotherapy should only be considered if it will improve survival more than several percentage points.
- We believe that caring for older patients is best done by a team of experts including oncologists, geriatricians, and other support staff.

TABLE 1. Randomized Trials of Hormonal Therapy and Breast-Conserving Surgery with or without Radiation Therapy in Older Women

Trial (No. of Patients)	Inclusion Criteria	Locoregional Recurrence without RT	Locoregional Recurrence with RT	p Value	Overall Survival Difference
CALGB[9] (636)	Age 70 and older	10% at 10 yr	2% at 10 yr	< 0.001	Not significant
	T1, HR+/unknown				
	Negative nodes				
Princess Margaret[59] (749)	Age 50 and older, T1/2, N0 (cN0 if older than 65, pN0 if younger than 65), no chemotherapy	17.6% at 8 yr	3.5% at 8 yr	< 0.001	Not significant
PRIME II[60] (1,326)	Age 65 and older, T size up to 3 cm, N0	2.7% at 5 yr	0.6% at 5 yr	0.004	Not significant
ABCSG[61] (869)	Postmenopausal, T size up to 3 cm, HR+, N0, grade 1/2	5.1% at 5 yr	0.4% at 5 yr	< 0.001	Not significant

Abbreviations: RT, radiation therapy; CALGB, Cancer and Leukemia Group B; HR, hormone receptor.

endocrine therapy in older women was associated with a small but statistically significant benefit in local control, but that radiation therapy did not improve overall survival or distant disease-free survival. The lack of survival benefit is not a result of less healthy patients being preferentially enrolled in the studies. Of note, a comparison of expected all-cause mortality between the general population and that seen in the CALGB 9343 trial showed that the women enrolled in this trial had better than average life expectancy, even with early-stage breast cancer.[9]

The National Surgical Adjuvant Breast and Bowel Project B-21 study analyzed the effect of radiation therapy alone, endocrine therapy with tamoxifen, and both treatments in women of all ages with cancers 1 cm or smaller in size; the trial did not include an arm in which patients received neither endocrine nor radiation therapy.[16] In this study, 5% of women discontinued tamoxifen or placebo because of side effects, and 11% withdrew for other reasons. Endocrine therapy alone is associated with side effects, and one large study showed that discontinuation of endocrine therapy was more likely for women older than age 65 than for those ages 55 to 65.[17]

Without a survival or distant disease-free benefit associated with radiation therapy in randomized trials among older women with early-stage breast cancer, the key question is whether a patient is willing to trade the improved local control afforded by radiation with its inconvenience, potential side effects, and cost. Radiation therapy is generally well tolerated in older women[18] but can be associated with rare but serious side effects such as secondary malignancies and cardiac toxicity. The risk of radiation-induced malignancy decreases with increasing patient age and is associated with a latency period of usually at least 5 to 20 years.[19] Likewise, although the risk of radiation-induced cardiac toxicity is higher among women with pre-existing cardiac risk factors, a majority of cardiac events (i.e., myocardial infarction, coronary revascularization, or death from ischemic heart disease) occur 10 years or more after radiation exposure.[20] Moreover, both the risks of secondary malignancies and cardiac toxicity appear to be decreasing with modern breast radiation techniques.[19,21] The assessment of life expectancy is critical in de-

termining the potential magnitude of benefit associated with radiation therapy versus the potential for toxicity, a measure not used in randomized trials.

The inconvenience associated with receipt of radiation therapy can be lessened in the older patient with omission of a boost and hypofractionation, which can reduce the daily treatment span by almost one-half. The European Organisation for Research and Treatment of Cancer conducted a randomized trial of 5,318 patients to study the benefit of adding a 16-Gy boost to the lumpectomy site after 50 Gy of whole breast radiation therapy.[22] The use of a boost reduced local recurrence at 10 years by 41% at the expense of increased breast fibrosis. However, similar to the pattern revealed in the EBCTCG meta-analysis, when the degree of reduction in local recurrence afforded by the boost was examined within age groups, the absolute magnitude of benefit diminished with increasing age because of a lower baseline risk of recurrence in older women. Women older than age 60 had a 7.3% and 3.8% risk of local recurrence at 10 years without and with the boost, respectively—a difference of 3.5%. This is in contrast to women age 40 and younger in whom the boost reduced the risk of local recurrence from 23.9% to 13.5%, a difference of 10.4%.

In addition to omission of a boost, hypofractionation, which reduces the total number of treatments can decrease the burden associated with receiving radiation therapy. Recently, mature data have revealed that the use of hypofractionation is as effective as conventional treatment schedules. Whelan et al randomly selected 1,234 women with early-stage breast cancer treated with breast-conserving surgery to receive whole breast radiation using a 5-week schedule (200 cGy per fraction for 25 treatments) versus a hypofractionated 3-week schedule (266 cGy per fraction for 16 treatments).[23] No difference was seen in the risk of local recurrence at 10 years or in cosmetic outcome. Subset analyses revealed that the efficacy of hypofractionation was similar in both younger and older women. Likewise, the United Kingdom Standardization of breast radiotherapy (START)-B trial randomly assigned 2,215 women to a 5-week schedule (200 cGy per fraction for 25 treatments) versus a hypofractionated 3-week schedule (266 cGy per fraction for 15 treatments).[24] At a me-

dian follow-up of 9.9 years, there was no significant difference in the likelihood of local recurrence between the two treatment arms. Indeed, the absolute rate of local recurrence was slightly lower (by 1%, p = 0.21) and freedom from marked or moderate cosmetic change improved (hazard ratio [HR] 0.77; 95% CI, 0.66 to 0.89) in the hypofractionated arm. Unlike partial breast radiation and intraoperative radiation, which also reduce treatment length, boost omission and hypofractionation do not require additional equipment or training, potentially enabling patients to have fewer radiation visits in all radiation treatment centers.

A question that remains unanswered is whether tumor biology may be more relevant than patient age in determining the risk of local recurrence. A retrospective study of 1,434 patients treated with breast-conserving surgery and radiation therapy at three hospitals used immunohistochemistry and grade to divide the cancers into five tumor subtypes: Luminal A, Luminal B, Luminal-HER2, HER2, and triple negative.[25] The overall risk of local recurrence at 5 years was only 1.6%. However, in addition to patient age, tumor subtype was a highly significant predictor for local recurrence. Among patients older than age 64, the crude risk of local recurrence was under 0.5% for all subtypes, except those with triple-negative cancers where it jumped to 6.9%. An initial report of a randomized study of 769 women older than age 50 with early-stage breast cancer treated with endocrine therapy with or without radiation therapy reported a reduction in the risk of local recurrence with radiation therapy from 13.8% to 5% at a median follow-up of 10 years (p < 0.0001).[26] However, interestingly, among a subset of 304 patients in whom molecular subtyping was performed, those with Luminal A cancers did not derive benefit from radiation therapy as the risk of local recurrence was low even without radiation therapy. In these patients with Luminal A disease, there was a 5.5% risk without and 4.9% risk with radiation (p = 0.9). In contrast, those patients with Luminal B cancers had a higher baseline risk of local recurrence and a striking improvement in this risk with the addition of radiation therapy: 16.1% with tamoxifen alone and 3.9% with both tamoxifen and radiation (p = 0.05). It is likely that the lower likelihood of local recurrence in older patients is not because of age itself but that older patients are more likely to have cancers with more favorable subtypes.[27] Prospective trials that omit radiation in women with low-risk tumor subtypes are currently underway.

Estimation of the individual's risk of recurrence will improve with further molecular characterization of cancers and life expectancy, and functional age calculations can be used to put this risk into context for an individual patient. In addition, a careful assessment of comorbidity and other potential impediments to receiving radiation therapy, such as being a great distance from a radiation treatment facility, is necessary to balance these burdens associated with treatment with its potential benefits. Although radiation therapy is associated with increased treatment time, it may reduce the likelihood of mastectomy at a later date, when an older patient's functional status may become further compromised.[28] Therefore, the choice regarding radiation therapy needs to be made by

assessing a patient's preference for treatment outcomes—recurrence-free versus mastectomy-free survival relative to the treatment burden and potential risk of side effects. Future research aimed at enhancing patient comprehension about these tradeoffs will help facilitate informed decision making. In the interim, given the lack of survival benefit seen in randomized trials and small differences in local control, the decision to prescribe routine use of radiation therapy for older patients with low-risk biology or with significant comorbidity should be made on a case-by-case basis

ADJUVANT SYSTEMIC THERAPY

The decision to recommend chemotherapy to an older patient with early-stage breast cancer is complicated and requires knowledge of life expectancy, the risks and benefits of the proposed treatment, and the patient's and family's goals for treatment.[29] In general, for healthy older patients with estimated survivals of 10 years or more, state-of-the-art treatments similar to those used for younger patients should be recommended. Although older women have a higher frequency of less aggressive tumors such as hormone receptor–positive, HER2-negative tumors, as many as 25% to 30% of older patients have HER2-positive and triple-negative breast cancers, as well as more aggressive, genetically defined subtypes.[27] We suggest that before making any treatment decisions, whether for endocrine therapy or chemotherapy, the patient's life expectancy be calculated using readily available online calculators. The ePrognosis calculators are based on patient setting (e.g., community, nursing home, hospital) and estimate survivals from 6 months to up to 10 years; accurate estimates of life expectancy are crucial and take only a minimal amount of time, but it does require asking several questions related to function not usually obtained in the routine history and physical examination. For patients with an average life expectancy of less than 5 years, the value of adjuvant endocrine therapy and certainly chemotherapy is likely to be minimal except in the case of patients with extremely high-risk disease.

For clinical care, breast cancers in older patients can be divided into three subtypes: (1) hormone receptor positive and HER2 negative, the most common subtype accounting for approximately 70% of patients, 2) HER2-positive tumors, and 3) triple-negative tumors—the latter two each accounting for approximately 15% of tumors. In older patients with small hormone receptor–positive tumors, including those with hormone receptor–positive, HER2-positive tumors, endocrine therapy with either AIs or tamoxifen is the mainstay of treatment. Survival benefits are similar for both AIs and tamoxifen but overall risk of relapse is a few percent lower with AIs.[30] The toxicities of both tamoxifen and AIs are both well defined, with arthralgia, myalgia, and bone loss being the major toxicities for AI therapy, and endometrial cancer and venous thromboembolism the major side effects for tamoxifen. In general, AIs may be preferable as initial treatment in most older patients, because unlike tamoxifen, they are not associated with endometrial carcinoma and do not increase

TABLE 2. Recommendations for Adjuvant Systemic Therapy for Patients with Life Expectancies Longer Than 5 Years

Tumor Phenotype	Extent of Disease	Recommendation
Hormone receptor–positive and HER2 negative	All	Tamoxifen or aromatase inhibitor for most
	Node-negative	Consider genetic-based assay (recurrence score and others) when chemotherapy is a consideration
	1-3 nodes positive	Tamoxifen or aromatase inhibitor
	Four or more nodes	Consider chemotherapy and discuss if greater than 3% survival benefit at 10 years using online calculators
Triple negative		Consider chemotherapy if 3% of greater survival at 10 years
		Consider anthracycline and taxane regimens if survival benefit at 10 years is 3% greater than anthracycline or taxane regimens alone
HER2 positive	Small node-negative tumors	Consider paclitaxel and trastuzumab for most
	Larger node negative of node-positive tumors	Consider docetaxel, carboplatin, and trastuzumab because of more favorable toxicity profile compared to anthracycline, taxane, and trastuzumab combinations
	All	Tamoxifen or aromatase inhibitor for hormone receptor positive
		Calculate added value of chemotherapy and trastuzumab for patients with low-risk tumors and consider not recommending if survival benefit at 10 years less than 3%

the need for yearly gynecologic examinations in older women who have not had a hysterectomy. Although arthralgia and myalgia are less likely to be seen in older patients treated with AI therapy,[31] they can result in pain and functional loss and create a cause for discontinuing therapy. It is important to query older patients on either tamoxifen or AIs about their adherence and persistence with endocrine therapy. Numerous studies have shown that lack of compliance with the use of these medications is substantial, with approximately 50% of patients not completing 5 years of therapy.[17,32]

The absolute added value in improving survival with the addition of chemotherapy to endocrine therapy in older patients with hormone receptor–positive, HER2-negative tumors is highly dependent on the risk of tumor recurrence. In general, the majority of patients with node-negative hormone receptor–positive, HER2-negative tumors will derive little benefit from chemotherapy. The decision to consider chemotherapy in these patients is best made using multigene molecular assays such as the recurrence score or other assays, which can provide prognostic or predictive information.[33-35] For patients with positive nodes, chemotherapy is likely to be of small value for those with low recurrence scores and with one to three positive lymph nodes.[36,37] Those patients with four or more nodes should be considered for chemotherapy if their life expectancy exceeds 5 years. The majority of recurrences for patients with this phenotype are seen after 5 years, even though the hazard rate for recurrence is highest in the first 5 years. Patients with a life expectancy of less than 5 years, irrespective of nodal involvement, are not likely to derive any benefit from chemotherapy if they have hormone receptor–positive, HER2-negative tumors.

For older patients with triple-negative breast cancer and a life expectancy exceeding 5 years (the timeframe in which most of these tumors recur), the major systemic treatment consideration is chemotherapy. Several chemotherapy regimens are appropriate in these patients and can be roughly divided into anthracycline and nonanthracycline treatments.[38] We suggest using online calculators including Adjuvant! Online and Predict to help guide treatment decisions. Similar to our colleagues in the United Kingdom, we believe that chemotherapy should only be considered if there is at least a 3% to 5% improvement in 10-year overall survival and recommended only if survival benefit exceeds 5% at 10 years. Survival benefits of less than 3% are questionable, as the calculators have been verified mostly in younger patients and lack large samples of older patients, especially those treated with more aggressive anthracycline and taxane regimens. A recent study suggested that Adjuvant! Online overestimated the benefits of chemotherapy in older patients.[39] In general, regimens such as doxorubicin and cyclophosphamide[40] or docetaxel and cyclophosphamide[41] are preferred, unless the calculated benefit for anthracycline and taxane regimens are at least several percentage points higher. It has been previously shown that older patients with node-positive breast cancer treated with more aggressive chemotherapy regimens derive similar benefits as younger patients but with greater toxicity.[42,43] Anthracycline regimens are associated with increased risks of cardiac toxicity and, more importantly, the development of acute myelogenous leukemia (AML) and myelodysplasia (MDS).[43] Taxane regimens have substantial risks of peripheral neuropathy, a potential toxicity that can dramatically impede function and impair the quality of life of older patients.[44] The risks of cardiac toxicity and AML/MDS for anthracycline compared to nonanthracycline regimens detract from their potential benefits as calculated in online models. It is essential to get the patient's perspective when offering chemotherapy and to carefully inform patients and families of the potential for major toxicities. Acute and severe grade 3 and 4 toxicities can be reasonably estimated before starting chemotherapy,[45-47] and presenting these risks may be helpful in the treatment discussions with older patients.

For a few percent gain in survival, it is our experience that many older patients will decline chemotherapy if it is likely to affect their physical function.

Older patients with HER2-positive tumors can benefit greatly from chemotherapy and trastuzumab. Both patients with hormone receptor–positive and hormone receptor–negative tumors benefit, but the greatest absolute benefit is seen in those with a hormone receptor–negative, HER2-positive phenotype—the most aggressive phenotype for patients who do receive adjuvant systemic therapy. Recent data have suggested that a combination of weekly paclitaxel and trastuzumab for patients with stage I, node-negative disease provides outstanding disease control with an estimated relapse-free survival of 98% at 3 years.[48] More aggressive regimens should be considered for older patients with higher-risk node-negative (i.e., tumors greater than 2 cm) or node-positive HER2-positive breast cancer, including docetaxel, carboplatin, and trastuzumab, or anthracycline and taxane regimens with trastuzumab— because their overall survival benefits are similar.[49] A major concern when offering chemotherapy and trastuzumab to older patients is the risk for cardiac toxicity,[50] which is enhanced in anthracycline regimens. Before initiation of chemotherapy, patients should have estimation of left ventricular ejection fractions (LVEF) using either echocardiographic or nuclear medicine methods. Those patients with below-normal LVEF or those with normal cardiac function but other risk factors for heart disease should be referred to a cardiologist for consideration of prophylactic use of beta-blockers and/or angiotensin-converting enzyme inhibitors.[51] The use of anti-HER2 directed therapy alone or in addition to endocrine therapy in the adjuvant setting has not been adequately studied. Ongoing trials utilizing ado-trastuzumab emtansine as a single agent are in progress and focused on further minimizing cardiotoxicity while maintaining similar efficacy to current chemotherapy and trastuzumab regimens.[52]

For patients who present with large primary lesions or extensive locoregional disease but without distant metastases, neoadjuvant therapy can improve chances for breast conservation. For patients with hormone receptor–positive, HER2-negative tumors, neoadjuvant endocrine therapy can be extremely effective, possibly as effective as chemotherapy.[53] For those with triple-negative breast cancer and good life expectancy, anthracycline and taxane regimens can be used. For patients with HER2-positive disease, neoadjuvant therapy that includes pertuzumab in addition to trastuzumab provides the best chances for tumor reduction.[54,55] A summary of our recommendations for adjuvant systemic therapy is shown in Table 2.

CONCLUSION

Caring for older patients with cancer takes time and in our opinion is best done using a team of interested and informed specialists including surgical radiation and medical oncologists. In addition, other support staff such as counseling, palliative care, nutritional, and physical and occupational therapy are frequently integral to optimizing outcomes. Geriatric assessment can be learned and performed in a short period of time and can identify problems that, if addressed, may improve a patient's tolerance for treatment, quality of life, and perhaps survival.[56,57] The goals of therapy for seriously ill patients age 60 and older suggests that loss of physical or cognitive function is a major treatment-related concern.[58] This would likely be of even greater concern for 70- and 80-year-old patients. We believe that estimating life expectancy, performing the geriatric assessment to separate vulnerable from healthy older patients, and then using this information to optimize treatment based on the evidence of randomized trials will result in the best outcomes.

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BREAST CANCER

New Targets and Therapies for Triple-Negative Breast Cancer

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Triple-Negative Breast Cancer: Immune Modulation as the New Treatment Paradigm

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OVERVIEW

Recent studies of tumor lymphocytic immune infiltrates in breast cancer have suggested an improved prognosis associated with increasing levels of tumor-infiltrating lymphocytes (TIL). Triple-negative breast cancer (TNBC) is the breast cancer subtype that has the greatest incidence of patients with a robust tumor immune infiltrate, although it is still a minority of patients. Elevated levels of either intratumoral or stromal T cells are associated with an improved overall survival (OS) and disease-free survival (DFS) in TNBC as compared with other breast cancer subtypes. TNBC may be immunogenic for several reasons. Subtypes of TNBC have a significant number of genetic mutations, and the immune system may see the aberrant proteins encoded by these mutations as foreign. Moreover, TNBC is associated with a prognostic gene signature that also includes B cells. Antibodies secreted by B cells may bind to tumor antigens and amplify the adaptive immune response that has already been initiated in the tumor. New immune modulatory agents, including immune checkpoint inhibitors, have shown activity in immunogenic tumors such as melanoma and bladder cancer and have recently been tested in TNBC. The clinical response rates observed, patterns of response, and adverse event profiles are similar to what has been described in melanoma where this class of agents has already been approved for clinical use in some cases. Lessons learned in assessing the immunogenicity of TNBC, potential mechanisms of immune stimulation, and response to immune modulatory drugs lay the foundation for the development of immune-based therapies in all subtypes of the disease.

The immune system is controlled by a balance of cellular signals that both initiate immune responses and actively inhibit inflammation induced by immunity. The ability to suppress immunity is critical to protect normal tissues from collateral damage during pathogen-destructive immune responses. The cells of both the innate (neutrophils, monocytes, macrophages, and a host of antigen-presenting cells [APC]) and the adaptive (T and B lymphocytes) immune system are called on to respond to pathogens or other threats. Working in concert, innate immune cells are required for T cells and B cells to be able to identify immunogenic proteins (i.e., antigens in the environment). Further, innate immune cells produce cytokines that optimize lymphocytic function. The lymphocytes can then recognize cells expressing foreign proteins and kill those cells. The generation of adaptive immunity in the appropriate cytokine milieu allows for the development of memory cells: long-lived lymphocytes that remain in lymph nodes and readily respond to the specific threat if further exposure occurs.

Proinflammatory type I immunity is the immune response needed to eliminate cancer. In a type I immune response, CD4 T-helper (Th) lymphocytes, called Th1, secrete cytokines such as interferon-gamma (IFN-gamma) and TNF-alpha that activate and enhance the lytic function of CD8 T-lymphocytes. Cytokines produced by type I T cells induce the upregulation of costimulatory molecules on APC, of the innate immune system allowing those cells to more effectively present immunogenic proteins to the T cells. CD8 T cells are cytolytic, and once they dock on a target through interaction with antigenic peptide containing major histocompatibility complex (MHC) molecules on the surface of that target, they either induce cell senescence or directly lyse target cells via a series of enzymatic reactions.

Breast cancer is capable of stimulating the immune system. It is well defined that some breast tumors have substantial lymphocytic infiltration, and the more T cells found in the cancer, the more favorable the prognosis.[1] Most breast cancers, however, have been infiltrated with few or even no T cells.[2,3] Breast cancers have modest levels of lymphocytic infiltrates for many reasons. One is that the immune cells found in the tumor microenvironment of breast cancer are type II cells. The CD4 Th2 cells express cytokines such as interleukin (IL)-10 and IL-6, which dampen destructive immunity. Innate immune cells and high levels of regulatory T cells (Treg) in the type II environment secrete substances that both inhibit the function of CD8 T cells and prevent their migration to the tumor, producing only a limited number of less active CD8 T cells available to induce tumor regression. Breast cancer can secrete substances that influence APC to educate T

cells to become type II rather than type I cells.[4] Most antigens present in breast cancer are self proteins, and the portions of the proteins that are most likely to stimulate T cells induce a regulatory immune response.[5] Furthermore, 30% to 50% of all breast cancers have upregulated programmed death ligand 1 receptor (PD-L1) on the cell surface.[6] When PD-L1 binds with programmed cell death protein 1 (PD-1) on the surface of T cells, the lymphocytes become inactivated. These are just a few of the mechanisms by which robust type I immunity is prevented from developing in breast cancer.

Breast cancer subtypes differ in the level of immune infiltration observed in the tumor. More patients with TNBC fall into the category of having a robust tumor T-cell infiltrate than any other subtype. Hormone receptor–positive disease is the subtype associated with the least robust number of TIL. HER2-positive disease has also been shown to have a number of patients with significant TIL in their tumor. In HER2-positive breast cancer, the numbers of TIL can be further increased by treatment with trastuzumab.[7] However, the prognostic significance of a robust TIL response is most pronounced for the TNBC subtype.

TUMOR LYMPHOCYTIC INFILTRATES IN TRIPLE-NEGATIVE BREAST CANCER

The clinical importance of tumor immune infiltrates has been an emerging area of research in breast cancer, particularly in TNBC where increased immune infiltrate predicts both response to chemotherapy and improved survival.[8,9] Tumors that have greater than 50% lymphocytic infiltrate are called lymphocyte-predominant breast cancer (LPBC) and

have the best prognosis. Interestingly, TNBC is most likely to have LPBC.[2,10] The presence of LPBC has been shown to predict improved pathologic complete response (pCR) to neoadjuvant chemotherapy. LPBC is associated with a pCR of approximately 40%, whereas tumors with no lymphocytic infiltrate have a 4% pCR rate (OR 1.39; 95% CI, 1.08 to 1.78; p = 0.012).[1] Specifically, in TNBC, LPBC was an independent predictor for improved pCR in multivariate analysis (OR 2.17; 95% CI, 1.27 to 3.72; p = 0.005).[1] A meta-analysis of studies examining TIL and pCR in all breast cancers with TIL present in the pretreatment biopsy predicted a 2.5-times increased pCR rate in TNBC (OR 3.30; 95% CI, 2.31 to 4.73; p < 0.0001).[11] The presence of TIL has also been shown to predict an improved clinical outcome in TNBC. In a study of 256 triple-negative tumors, LPBC was associated with both an improved DFS (p = 0.018; hazard ratio [HR] 0.30; 95% CI, 0.11 to 0.81) and OS (p = 0.036; HR 0.29; 95% CI, 0.091 to 0.92), and when TIL were evaluated as a continuous variable, every 10% increase in TIL correlated with a 17% decrease in the risk of recurrence (p = 0.023; HR 0.83; 95% CI, 0.71 to 0.98) and a 27% decreased risk of death (p = 0.035; HR 0.73; 95% CI, 0.54 to 0.98).[2] Similar results from a study of 278 patients showed that 5-year OS of patients with TNBC with LBPC compared to those without TIL was 91% and 55%, respectively, (HR 0.19; 95% CI, 0.06 to 0.61; p = 0.0017) further emphasizing that high TIL predict a portion of patients with TNBC who do well in this otherwise poor outcome subtype.[8] When a meta-analysis of TIL was performed in almost 3,000 patients with TNBC with a median 113-month follow-up, increased TILs were associated with 30% reduction in risk of recurrence (HR 0.70; 95% CI, 0.56 to 0.87; p = 0.001), 22% decreased risk of distant recurrence (HR 0.78; 95% CI, 0.68 to 0.90; p = 0.0008), and a 35% decreased risk of death (HR 0.66; 95% CI, 0.53 to 0.83; p = 0.0003).[10] Although LPBC has been shown to predict benefit in TNBC, it has not been shown to predict improved OS or DFS in HR-positive or HER2-positive breast cancer.[2]

Although evaluation of TIL gives a global measure of lymphocytic immune infiltrate, it does not define the specific phenotype of populations of immune cells infiltrating the tumor, and these immune subsets may further define clinical outcome and guide further immune therapy. Triple-negative tumors have been evaluated for cytotoxic CD8 T-cell infiltrate, which has been shown to predict improved OS in breast cancers in general.[12] Intratumoral CD8 T-cell infiltration above the mean per high-powered field predicted a pCR of 46% compared with a low CD8 T-cell infiltration (15%; p = 0.002), with an increased intratumoral CD8/FOXP3 ratio independently predicting improved pCR (OR 5.32; 95% CI, 1.62 to 19.98; p = 0.005) in a study of 110 patients with TNBC after receiving neoadjuvant chemotherapy.[13] Furthermore, in multiple studies, the presence of CD8 T-cell infiltrate has been associated with improved survival in TNBC, although response with increasing levels of CD8 T-cell infiltrate has not been quantified as it has with LPBC. Improved relapse-free survival was found in a study of 448 triple-negative tumors either with intratumoral (p = 0.016) or stromal (p = 0.001) CD8^{+} T

cells. Improved disease-specific survival (p = 0.031; response rate [RR] 0.70; 95% CI, 0.5 to 1.0) was observed as well.[14] Similarly, CD8 T cells increased above the mean predicted improved disease-specific survival in 927 triple-negative breast tumors (p = 0.001; HR 0.35; 95% CI, 0.23 to 0.54).[15] Although TNBC is the subtype most associated with TIL, only a minority of patients' tumors demonstrate LPBC, suggesting immune modulatory therapy is needed to increase the adaptive immune infiltrate to levels necessary for survival benefit in the majority of patients with this breast cancer subtype.

POTENTIAL MECHANISMS OF IMMUNE STIMULATION IN TRIPLE-NEGATIVE BREAST CANCER

What makes TNBC more likely to be infiltrated with lymphocytes than other breast cancer subtypes? One potential mechanism is that TNBC is immunogenic because of genetic instability and increased mutations. Mutated genes may encode proteins that appear slightly different to the immune system. Peptide epitopes that contain a mutation and are presented to T cells in the MHC may be recognized as more foreign than nonmutated sequences. A recent study evaluating patients with metastatic melanoma treated with the CTLA-4 blocking monoclonal antibodies ipilimumab or tremelimumab demonstrated that the level of tumor mutational load was associated with the degree of clinical benefit from these immune modulators (p = 0.01).[16] The authors further evaluated a mutational signature consisting of specific peptide sequences that were shared across patients' tumors and predicted to bind with higher affinity to MHC. The neo-epitope signature demonstrated a stronger association between response and OS than mutational load alone.[16]

Tumors from patients with TNBC are more likely than other subtypes to demonstrate chromosomal instability and, potentially, mutations.[17] In a survey of over 300 breast tumors, although chromosomal instability predicted worse prognosis for most subtypes, there was no clinical effect observed for patients with TNBC. Recent investigations have performed deep sequencing on 104 cases of TNBC and demonstrated that tumor gene mutations were highly variable with the median number of somatic mutations about 50, but only one-third of the mutations identified were expressed—a requirement for immune recognition.[18] These data suggest that although tumor-specific mutations may play a role for the enhanced immunogenicity of TNBC, there must be other contributing factors.

Compared with other breast cancer subtypes, TNBC has also been associated with a positive prognostic signature that is B cell–specific. B cells are mediated by Th2 T cells and, when present in breast cancer, have been associated with increased cell growth.[19] Evidence suggests, however, that tumor-targeting B cells may enhance antitumor immunity by stimulating antibody-dependent cell-mediated cytotoxicity, a mechanism of tumor cell death initiated by IFN-gamma secreting natural killer (NK) cells.[20] Several investigators have identified a meta-gene signature that includes a B-cell/plasma cell component associated with improved survival, particularly in the basal cell phenotype of TNBC.[21] A ratio of

high B cell and low IL-8 identified one-third of TNBC with good prognosis (HR 0.37; 95% CI, 0.22 to 0.61; p < 0.001). The B-cell signature was shown to increase the predictive value of other prognostic signatures for TNBC when used in combination.[22] Finally, recent studies have used mRNA sequencing to assess the degree of somatic hypermutations in B cells thus evaluating B-cell population diversity in breast tumors. The presence of clonal B-cell populations in TNBC—indicating an evolving adaptive immune response—was associated with an improved metastasis-free and progression-free survival.[23] Antibodies of multiple different specificities binding to proteins expressed in TNBC could draw increased numbers of innate immune cells capable of processing and presenting tumor antigens to T cells to the tumor bed. Moreover, the type I cytokines produced by the NK cells recruited via antibody Fc receptors could further activate an adaptive immune response.

Although the majority of TNBC requires immune modulatory therapies that would increase TIL, those patients with high levels of TIL might benefit from the use of immune checkpoint inhibitor agents to further augment the lymphocytic response to beneficial therapeutic effect.

IMMUNE CHECKPOINT INHIBITORS IN TRIPLE-NEGATIVE BREAST CANCER

As TNBC seems to be the subtype most associated with the presence of TIL, clinical studies have attempted to assess the utility of immune checkpoint inhibitor therapy as a potential effective treatment for the disease. Immune checkpoint proteins are present on normal tissues, cells of the innate immune system, and lymphocytes. When a T cell interacts through its immune checkpoint receptor protein (e.g., PD-1), with the companion receptor on an APC or tumor cell (e.g., PD-L1), that T cell will be inactivated. Immune checkpoint proteins become upregulated in the presence of inflammation and, as stated above, are a part of the host's natural defenses limiting immune-mediated destruction of normal tissues.

Monoclonal antibodies have been developed that will block specific immune checkpoint proteins. Three of these antibodies are approved by the U.S. Food and Drug Administration for the treatment of metastatic melanoma and are used as a standard of care for some patients. Ipilimumab blocks CTLA-4 and does not allow the T cell to interact with the receptor via CD28 on its cell surface. Nivolumab and pembrolizumab are antibodies that will block PD-1 on the surface of T cells and prevents those T cells from interacting with PD-L1. Monoclonal antibodies that will block PD-L1 are also being studied in clinical trials.

Investigations evaluating the presence of PD-1 on TIL and PD-L1 on tumor cells in breast cancer have found that immune checkpoint proteins are upregulated in many breast cancers, particularly the triple-negative subtype. The reported incidence of expression is highly variable and may depend on methods used to assess immune checkpoint proteins as well as the quality of reagents available to interrogate tissues for protein expression. One study of 116 breast cancers

TABLE 1. Unique Characteristics of Immune Checkpoint Inhibitor Therapy

Clinical Observation	Rational
Slower time to response than observed with standard cytotoxic agents	T cells proliferate and divide in response to antigen and immunomodulation. T cells need time to expand to the numbers required for an influence on tumor growth.
Initial increase in tumor size followed by regression	Trafficking T cells can infiltrate the tumor in high enough numbers to cause inflammation and swelling—known as pseudoprogression.
Immune-related adverse events	General immune stimulators, such as checkpoint inhibitors, can induce immunity reactive to normal tissues that are immunologically active (e.g., skin, gut).
Prolonged periods of disease stabilization	T cells and tumor cells can exist in an immunologic equilibrium in which T cells control tumor growth but do not eradicate cancer.
Mixed responses with some lesions responding while other metastatic sites progress	This represents the development of immunologic remodeling where some metastatic deposits have developed mechanisms of immune resistance.

found that PD-1 was expressed on the surface of 50% of TIL, PD-L1 was present in 45% of breast cancers, and concurrent expression of both occurred in 29%.[24] TILs expressing PD-1 were more commonly found in the triple-negative subtype (70%) than in the rest of the subtypes (25% to 44%, p < 0.001). PD-L1 was also more commonly expressed in triple-negative disease than the other subtypes (59 vs. 33%, p = 0.017). In this study, PD-1-positive TILs were associated specifically with the presence of p53 mutations in TNBC potentially representing a neoepitope signature, whereas there was no correlation of the expression of PD-L1 and mutational load. An additional study analyzing PD-L1 gene expression and using data from the Cancer Genome Atlas found that TNBC showed significant upregulation of PD-L1 as compared to other subtypes (p < 0.001). Evaluation by tissue microarray demonstrated 19% of 105 patients with TNBC expressed PD-L1.[25] Data such as these has supported the study of immune checkpoint inhibitors in TNBC.

One of the first completed clinical trials of a PD-1 monoclonal antibody (pembrolizumab) in TNBC was reported at the 2014 San Antonio Breast Cancer meeting by Nanda et al.[26] The phase Ib study enrolled 32 patients with TNBC who had recurrent or metastatic disease (47% of which had more than three lines of previous chemotherapy) with PD-L1 expression in their tumor (58% of all patients screened had PD-L1-positive tumors). Pembrolizumab was administered 10 mg/kg intravenously every 2 weeks, and treatment could continue indefinitely as long as patients were stable and their disease was not clearly progressing as assessed by RECIST v1.1 every 8 weeks. Treatment with PD-1 blockade was tolerable, with 56% of patients reporting an adverse event, but only 16% with grade 3–5 toxicity. There was one treatment-related death caused by disseminated intravascular coagulation. The overall RR was 19% (27 patients were evaluable for response) with one (4%) complete response, four (15%) partial responses, and seven patients (26%) with stable disease. Of note, the median time to response was 18 weeks (range, 7 to 32) underscoring the unique kinetics of response seen with immune modulation as compared with conventional cytotoxic agents. Other unique characteristics of immune checkpoint inhibitor therapy are shown in Table 1.

Initial data from a phase I study of an anti-PD-L1 mono-

clonal antibody, MPDL3280A, in metastatic TNBC was also reported.[27] To date, Emens et al have treated 12 patients with PD-L1-positive disease. Grade 3– 4 toxicities occurred in 8% of patients (one renal insufficiency). Although immune-related adverse events have been reported with the use of immune checkpoint inhibitor agents (Table 2), only one patient in this study demonstrated grade 2 pyrexia that was potentially attributable to immune activation. In general, immune-related adverse events occur in a minority of patients. There were no toxicity related deaths. Despite the fact that over 90% of patients had been previously treated with more than two prior regimens and one-third of those enrolled had visceral metastases, the overall RR was 33% in the nine patients evaluable for efficacy (one complete response and two partial responses). All responses were seen within the first 6 weeks of treatment.

CONCLUSION

Population-based studies of TIL in breast cancer have underscored that the disease is immunologically active, with TNBC showing the greatest benefit from an endogenous immune response. Initial studies of immune modulation clearly indicate that TNBC is responsive to newly developed immuno-oncology agents that have been clinically effective in classic immunologic tumors such as melanoma. This observation furthermore may allow immune-based therapies to move rapidly from clinical development to standard of care in TNBC. Rational combinations to further enhance immunity should be tested in all subtypes of breast cancer. Identifying the components of the tumor immune environment that improve prognosis in breast cancer may also identify methods

TABLE 2. Immune-Related Adverse Events

Site	Adverse Event
Skin	Rash, pruritus, hives, sun sensitivity
Liver	Elevated liver function tests, hepatitis
Endocrine	Headache, visual field changes, adrenal insufficiency, hypopituitarism, hypothyroid, hypophysitis
Gut	Diarrhea, colitis

to modify the tumor immune environment to improve prognosis for tumors that do not contain TIL. For TNBC, controlling tumor growth with immunologically active conventional chemotherapies in combination with immune checkpoint inhibitors could increase response rates. For patients with limited T-cell infiltration vaccine priming before or concurrent with immune checkpoint inhibitors may result in clinical benefit. A better understanding of the immune microenvironment and why certain subtypes of breast cancer are more, or less, immunogenic will speed the clinical application of immune modulatory therapies to the benefit of all patients with breast cancer. Lessons learned in triple-negative disease is a great start to improved outcomes for all.

Disclosures of Potential Conflicts of Interest

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Triple-Negative Breast Cancer: Molecular Subtypes and New Targets for Therapy

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OVERVIEW

Triple-negative breast cancer (TNBC) is a molecularly diverse disease. This heterogeneity has limited the success of targeted therapy in unselected patients to date. Recent transcriptional analysis has divided TNBC into transcriptionally similar subtypes that may have different sensitivity to neoadjuvant chemotherapy and targeted therapy. At present, chemotherapy is the mainstay of treatment for early-stage and advanced TNBC; however, several actionable targets show promise in preclinical studies. Novel therapeutic strategies are currently being tested in phase II and phase III trials and will likely require patient stratification before therapy. Examples of these tailored approaches include poly(ADP-ribose) polymerase inhibitors for *BRCA*-mutated TNBC, antiandrogens for androgen receptor (AR)–positive TNBC, fibroblast growth factor receptor (FGFR) inhibitors for TNBC harboring FGFR amplifications, and gamma-secretase inhibitors for TNBC with mutations in the PEST domain of NOTCH proteins. Treatment of TNBC based on molecular subsets represents a potential algorithm for the future. Well-designed clinical trials with incorporation of integrated biomarkers are necessary to advance the development of molecularly targeted therapy for different subgroups of TNBC.

TNBC is a heterogeneous collection of breast cancers lacking expression of estrogen receptor (ER), progesterone receptor (PR), and HER2 amplification. Together these tumors represent approximately 15% of all breast cancers, preferentially affect young women, and are more frequent in women of African and Hispanic descent.[1,2] Patients with TNBC have a higher risk of both local and distant recurrence, and metastasis is more likely to occur in the brain and lungs rather than bone compared to other subtypes. The overwhelming majority of metastases of TNBC occur within the first 3 years following diagnosis, and patients who have not recurred during this time have similar survival rates as do patients with ER-positive breast cancers.[3]

There is a well-established association between deleterious *BRCA1* mutations and the risk of developing TNBC, with lifetime risks reaching as high as 50% to 85%. BRCA1 encodes an E3 ubiquitin protein ligase essential for homologous recombination mediated-repair of DNA double-stand breaks. Retrospective analysis and previous trials have shown striking pathologic complete response (pCR) rates in *BRCA1* mutation carriers (72% to 90%) with single-agent neoadjuvant DNA-crosslinking platinum salts (e.g., cisplatin).[4,5] In the metastatic TNBC setting, a phase III study (Triple Negative Breast Cancer Trial, TNT) of carboplatin area under the curve (AUC) 6 every 3 weeks compared with docetaxel 100 mg/m^2 every 3 weeks as first-line treatment was conducted in 376 women with assessment of *BRCA* status.[6] In the overall population, at a median follow-up of 11 months, outcomes were similar in terms of response rate (31.4% vs. 35.6%; p = 0.44), progression-free survival (PFS, 4.5 vs. 3.1 months), and overall survival (OS, 12.3 vs. 12.4 months), between the docetaxel and carboplatin arm, respectively. However, *BRCA* mutant carriers who received carboplatin compared with docetaxel experienced a significantly greater response (68% vs. 33.3%; 95% CI, 6.3 to 63.1; p = 0.03). The median PFS for patients with *BRCA1/2* mutations in the carboplatin group was 6.8 months compared with 3.1 months for non-*BRCA* mutation carriers, and 4.8 months and 4.6 months, respectively, among patients with and without *BRCA1/2* mutations treated with docetaxel. These data strongly support the use of a platinum agent for metastatic TNBC with *BRCA* mutations.

Although germ-line *BRCA1* mutations are more frequently observed in TNBC,[7] only a few recurrently mutated genes across the heterogeneous group of tumors make up TNBC. Recent sequencing efforts have shown the most frequent somatic mutations occur in TP53 (62%) and PIK3CA (10%), the gene encoding the p110alpha catalytic subunit of phosphatidylinositol-3 kinase (PI3K).[8,9] In addition to diverse mutations, TNBC tumors also display heterogeneity at the copy number and expression level with several clusters containing basal-like tumors.[10] Unlike ER-positive and HER2-amplified breast cancers, the lack of high frequency oncogenic driver mutations in TNBC means limited molecularly targeted treatments for this disease.

Neoadjuvant chemotherapy has proven efficacy in the treatment of TNBC and the regimens include combinations of anthracyclines, alkylating agents, taxanes, and platinum salts. Patients treated with neoadjuvant chemotherapy who experience a pCR at the time of surgery have significant improvements in both disease-free survival (DFS) and OS compared to patients with residual invasive disease.[11] The latter patients have a much poorer prognosis and are six times more likely to have recurrence and 12 times more likely to die.[12,13] Currently, there are no clinically actionable biomarkers to predict which patients with TNBC will experience a pCR.

MOLECULAR HETEROGENEITY OF TNBC

TNBC show a remarkable diversity of histologic patterns and subtypes. Although majority are high-grade invasive ductal carcinomas, a small subset has distinct pathologic features and indolent clinical behavior. Rare cases of adenoid cystic carcinomas and secretory carcinomas share common recurrent chromosomal translocations, resulting in oncogenic chimeric fusions (MYB-NFIB and ETV6-NTRK3, respectively).[14,15] In addition, several TNBC have atypical medullary and metaplastic histologies. Medullary carcinomas are characterized by infiltrating carcinomas with circumscribed pushing borders, dense peripheral lymphoid infiltrate, and have favorable outcome, whereas metaplastic carcinomas display differentiation toward squamous epithelium with mesenchymal components and cells displaying spindle, chondroid, osseous, or rhabdoid morphologies.[16,17]

Given the diverse pathologic classifications, one would predict that TNBC have a diverse array of biologic subtypes that could be revealed by transcriptional profiling. Initial global transcriptional studies showed TNBC to largely display basal-like gene expression.[18] This observation led many

investigators to consider basal-like breast tumors and TNBC to be relatively synonymous. The uniform basal-like gene expression pattern in TNBC is largely a result of the significant transcriptional differences between hormonally driven cancers and TNBC.[19] However, when analyzed independent from ER- and HER2-positive cancers, TNBC have quite heterogeneous gene expression patterns that can be used to classify the tumors into distinct subtypes.[20,21]

SUBTYPES OF TNBC

Using gene expression analyses from 386 tumors, we recently identified six distinct TNBC subtypes, each displaying unique biologies.[20] The TNBC molecular subtypes include two basal-like (BL1 and BL2), an immunomodulatory (IM), a mesenchymal (M), a mesenchymal stem-like (MSL), and a luminal AR (LAR) subtype. The BL1 subtype is characterized by elevated cell cycle and DNA damage response gene expression, while the BL2 subtype is enriched in growth factor signaling and myoepithelial markers. Both M and MSL share elevated expression of genes involved in epithelial-mesenchymal-transition (EMT) and growth factor pathways, but the MSL subtype has decreased expression of genes involved in proliferation. Consistent with the dedifferentiated mesenchymal gene expression pattern is the recent analysis of metaplastic breast cancers showing the majority of chondroid and spindle cell carcinomas to be of the MSL subtype.[17] The IM subtype is composed of immune antigens and genes involved in cytokine and core immune signal transduction pathways. The LAR subtype is characterized by luminal gene expression and is driven by the AR. Comparison with the intrinsic subtypes demonstrated that BL1, BL2, IM, and M are largely composed of basal-like subtype, while MSL has a large fraction of normal-like and LAR mostly composed of luminal and HER2 subtypes.[19] In addition to the intrinsic subtypes, a claudin-low subtype has recently been described and is enriched for EMT markers, immune response, and cancer stem cell–like genes.[22] This claudin-low subtype is mostly composed of M and MSL TNBC subtypes.[19]

In addition, we identified representative cell lines and demonstrated differential sensitivity to chemotherapy and targeted agents. BL1 cell lines are sensitive to genotoxic agents, LAR cell lines have differential sensitivity to the LAR antagonist bicalutamide and PI3K inhibitors, mesenchymal cell lines are more sensitive to the multifamily tyrosine kinase inhibitor dasatinib, and M cell lines display some sensitivity to PI3K/mTOR inhibitors. Subtyping of breast tumors from The Cancer Genome Atlas (TCGA) resulted in identification of 163 tumors and analysis of the clinical data associated with TNBC tumors demonstrated that the median OS and DFS of patients with BL1, IM, and MSL subtype tumors were nearly double that of patients with BL2, LAR, and M tumors.[23] Further, patients with tumors of the IM subtype had the best outcome. Analysis of the gene expression data from the IM subtype and identification of transcripts associated with lymphocytes suggests that the IM tumor samples may contain

tumor-infiltrating lymphocytes (TILs). The favorable outcome of patients with TNBC with higher levels of TILs associated with their tumors has recently been demonstrated in two adjuvant phase III trials.[24]

A similar transcriptional analysis was recently performed on a smaller cohort of 84 patients, and investigators identified four stable TNBC subgroups associated with distinct clinical outcomes.[21] They defined these subtypes as "luminal/androgen receptor (LAR)," "mesenchymal (MES)," "basal-like/immune-suppressed (BLIS)," and "basal-like/immune activated (BLIA)" groups. Similar to the previous study, TNBC patients with tumors expressing immune component features had the best outcome. Between the two studies there is clearly evident overlap between MSL and MES, IM and BL1 with BLIA, M with BLIS, and the two LAR subtypes. In summary, these data show that reproducible and distinct transcriptional subtypes can be unmasked when TNBC samples are analyzed in the absence of ER- and HER2-expressing tumors and as sample size is increased there will likely be additional unique subtypes revealed.

Despite the rather aggressive clinical behavior of TNBC, approximately 30% of patients with TNBC benefit from chemotherapy. In a retrospective reanalysis of pretreatment biopsies, TNBC molecular subtypes were predictive of response to neoadjuvant anthracycline and cyclophosphamide followed by taxane.[25] This study showed BL1 had the highest pCR rate (50%) at time of surgery and BL2 and LAR had the lowest (0% and 10%, respectively). Similar to the initial classification, patients with LAR subtype were significantly older at diagnosis, and recent preclinical data suggest that these patients may benefit from antiandrogen or PI3K inhibitors.[26] We recently demonstrated that PIK3CA kinase domain mutations are a frequent event in AR-positive TNBC tumors relative to the other subtypes (40% vs. 4%), and targeting of AR in LAR cells increases sensitivity to PI3K inhibitors. These data suggest that although there are few genomic alterations shared by TNBC as a whole, individual subtypes may be enriched in select somatic alterations, several of which may afford opportunities for preclinical discovery and translation to clinical investigation.

NOVEL APPROACHES FOR TREATMENT OF TNBC

Chemotherapy at present is the main treatment for patients with TNBC. No specific targeted agent has U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA) approval to treat TNBC in the adjuvant, neoadjuvant, or metastatic settings. This article discusses the most recent data on promising and novel targeted, nonimmunotherapeutic approaches currently under evaluation for TNBC.

Poly(ADP-Ribose) Polymerase Inhibition

The PARP enzyme plays an important role in the repair of DNA single-strand breaks via the base-excision repair (BER) pathway. PARP protein binds directly to sites of DNA damage and recruits other DNA repair enzymes. In normal cells,

BER and homologous recombination (HR, repair of DNA double-strand breaks) are both available to repair damaged DNA. In cancer cells of *BRCA1* or *BRCA2* mutation carriers, where HR is nonfunctional, PARP inhibition leads to an accumulation of DNA single-strand breaks that degenerate into double-strand breaks and result in cell death, as the cells are unable to repair DNA damage by either BER or HR.[27] This "synthetic lethality" has been demonstrated in several preclinical studies where BRCA-deficient cells are markedly sensitive to PARP inhibitors.[28,29] The prevalence of *BRCA1* or *2* mutations in TNBC is estimated to be between 10.6% and 19.8%.[7,30] Since genomic instability is common to both *BRCA*-mutated cancers and TNBC, investigators have tried to expand BRCA-deficient tumors to include those TNBC with transcriptional profiles similar to BRCA-mutants, referred to as BRCAness.[31] These observations have led to multiple efforts in evaluating PARP inhibitors as monotherapy or in combination with cytotoxic agents in the treatment of both mutant and sporadic TNBC.

Olaparib was the first oral PARP inhibitor to be approved under accelerated approval by the FDA in December 2014 as single-agent treatment of patients with a deleterious or suspected deleterious germ-line *BRCA* mutated advanced ovarian cancer, treated with three or more prior lines of chemotherapy. Additionally, the EMA recommended approval of olaparib for use in the maintenance treatment of platinum-sensitive relapsed *BRCA*-mutated (germ line and/or somatic) high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer in complete response or partial response to platinum-based chemotherapy, and has been granted marketing authorization by the European Commission. The side effects of PARP inhibitors are mild and include fatigue, nausea, and vomiting.

In breast cancer, the antitumor activity of PARP inhibitors is evidenced in several metastatic trials, and the most compelling subset to benefit are the patients that harbor *BRCA*-mutations. Several phase II trials of PARP inhibitors as monotherapy have been conducted in patients with metastatic breast cancer (MBC). Tutt et al evaluated olaparib in 54 patients with MBC and germ-line *BRCA* mutations who were treated previously with a median of three prior chemotherapy regimens.[32] Two cohorts were enrolled. One group (50% triple negative) was treated with olaparib 400 mg twice daily and the second group (64% triple negative) with 100 mg twice daily. In patients with TNBC, the response rate was 54% (7/13) in the higher-dose group, and 25% (4/16) in the lower-dose group; all were partial responses. Disease stabilization was 31% and 44%, respectively. This proof of concept study confirmed activity in *BRCA*-mutated TNBC, as well as in patients who were ER positive and HER2 positive. In an international, multicenter phase II study by Kaufman et al, 298 patients with *BRCA1* and *BRCA2*-associated cancers, including breast, ovarian, pancreatic, and prostate, were treated with olaparib 400 mg twice daily.[33] In the MBC cohort of 62 patients, the overall response rate was 12.9% (95% CI, 5.7% to 23.9%; all partial responses). In the 30 patients with ER-negative tumors, the response rate was 13.3% (95% CI,

3.8% to 30.7%). The lower efficacy in this trial may be a result of a more pretreated population in which the median number of prior chemotherapies was 4.6 and a higher percentage of patients with prior platinum exposure. In another multi-center trial, no responses were observed in 15 patients with non-*BRCA* TNBC who received olaparib 400 mg twice a day, indicating that single-agent PARP inhibitor is not likely to be a treatment approach for sporadic TNBC.[34]

Veliparib, another oral PARP 1 and 2 inhibitor, has been extensively evaluated in combination with several chemo-therapeutic agents as a chemopotentiator. Isakoff et al con-ducted a study in 41 patients with MBC who had at least one prior cytotoxic regimen and were given veliparib 30 mg orally twice daily day 1 through 7 (originally started at 40 mg but reduced secondary to grade 4 thrombocytopenia) and te-mozolomide 100 mg/m^2 orally daily day 1 through 5 every 28 days.[35] The response rate in *BRCA*-mutation carriers was 37.5% (3/8), including one complete response and two partial responses, and there were no responses in non-*BRCA* carri-ers (0/33). To date, the data suggest that a monotherapy treat-ment strategy for PARP inhibitors is not active in sporadic TNBC, but preferentially active in *BRCA*-mutated breast cancer. The combination of a PARP inhibitor and DNA-damaging agents for potentiation may still have a role in a specific subset of sporadic TNBC. Given the observed activity of PARP inhibitors in these studies, major phase III clinical trial efforts are underway to evaluate the benefit of PARP in-hibitors in the adjuvant and neoadjuvant settings.

OlympiA (National Surgical Adjuvant Breast and Bowel Project [NSABP] B-55/BIG 6-13, NCT02032823) is a ran-domized, double-blind, placebo-controlled phase III study to evaluate the effect of adjuvant treatment with olaparib in 1,320 patients with germ-line *BRCA1/2* mutations and TNBC who have completed definitive local treatment.[36] This is a global, collaborative effort led by NRG Oncology and the Breast International Group and sponsored by the National Cancer Institute and AstraZeneca. The primary endpoint is invasive DFS. Randomization is 1:1 to either 12 months treat-ment with olaparib 300 mg orally twice daily or matching placebo. Eligible patients are those who did not achieve a pCR following at least six cycles of neoadjuvant chemother-apy followed by surgery or patients with either axillary node-positive disease or axillary node-negative disease with a primary tumor larger than 2 cm, who have undergone sur-gery and have completed at least six cycles of adjuvant che-motherapy. This is a unique trial targeting a rare population, with the potential to change the current adjuvant standard of care of observation for high-risk primary TNBC with *BRCA* mutations.

Another phase III clinical trial (M14-011, AFT-04, ABCSG 44, GBG 81, GEICAM/2014-02, NSABP B56-I, USO 12152, NCT02032277) is the first to evaluate the efficacy of veliparib in combination with chemotherapy for neoadjuvant treat-ment of TNBC.[37] This is a randomized, placebo-controlled, double-blind trial enrolling women presenting with clinical stage T2-4N0-2 or T1N1-2 triple-negative disease, who are candidates for potentially curative surgery. They will be ran-

domly assigned in a 2:1:1 ratio to one of three neoadjuvant treatment arms: (arm A) weekly paclitaxel 80 mg/m^2 for 12 weeks, carboplatin (AUC6), veliparib 50 mg orally twice daily followed by doxorubicin and cyclophosphamide (AC); (arm B) weekly paclitaxel 80 mg/m^2 for 12 weeks, carboplatin (AUC6), placebo followed by AC; or (arm C) weekly pacli-taxel 80 mg/m^2 for 12 weeks, placebo, placebo followed by AC. All patients must have documented *BRCA* germ-line mutation testing. The primary endpoint is pCR in the breast and lymph node. The trial seeks to accrue 624 subjects in about 200 sites. This is another global collaboration with sev-eral groups including the Alliance for Clinical Trials in On-cology, Austrian Breast and Colorectal Cancer Study Group, German Breast Group, Grupo Espanol de Investigacion en Cancer de Mama, NSABP Foundation, and US Oncology, and it is sponsored by Abbvie. The results of this study will help answer the question of the utility of carboplatin with and without a PARP inhibitor in TNBC with and without *BRCA* mutations. Results from these studies will hopefully lead to the availability of PARP inhibitors in routine clinical practice for patients with *BRCA*-mutated breast cancers and TNBC with DNA repair pathway defects.

More effective treatment strategies are needed for sporadic TNBC. Other approaches are being developed to sensitize sporadic TNBC to PARP inhibition. One example is an on-going clinical trial (NCT01623349) that is evaluating olapa-rib and BKM120 (buparlisib) or BYL719, PI3-kinase inhibitors, in advanced sporadic TNBC and high-grade se-rous ovarian cancer.[38] Another trial (NCT01434316) is com-bining veliparib and dinaciclib, a cyclin-dependent kinase inhibitor (CDK) inhibitor, where the hypothesis is that CDK inhibition sensitizes BRCA-proficient breast cancers to PARP inhibition.[39] After the phase I dose-finding portion, the study will enroll patients with *BRCA*-mutated and non-mutated advanced breast cancer in a dose-expansion cohort. These combinatorial approaches of PARP inhibitor and other targeted agents are promising strategies that may ex-pand the clinical utility of PARP inhibitors to sporadic TNBC.

Inhibition of the PI3K/AKT/mTOR Pathway

The PI3K/AKT/mTOR pathway mediates multiple cellular processes including cell survival, metabolism, proliferation, motility, migration, invasion, and angiogenesis.[40] Hyperacti-vation of the PI3K/AKT signaling pathway is frequent onco-genic alteration in TNBC, occurring in approximately 10% of patients.[9] Activating PIK3CA mutations are the most frequent in TNBC.[41] Other alterations that result in PI3K pathway activation include loss of the tumor suppressor phosphatases inositol polyphosphate 4-phosphatase type II (INPP4B) and loss of phosphatase and tensin homolog (PTEN).[9,42] Additionally, amplification of AKT and translo-cation of AKT3 occurs in a small subset of TNBC.[43] The PIK3CA activating mutations appear to be enriched in mes-enchymal and LAR molecular subtypes.[20] Targeting the PI3K/AKT pathway represents a compelling and rational po-tential treatment strategy for a subset of TNBC.

Ipatasertib (GDC-0068) is a novel, selective, ATP-competitive small molecule inhibitor of all three isoforms of the serine/threonine kinase AKT.[44] It shows single-agent activity in several xenograft models with AKT pathway activation via PTEN loss and/or PIK3CA mutation, including breast. In a phase Ib study of ipatasertib and paclitaxel in patients with MBC, the most commonly reported side effects were diarrhea, nausea, fatigue, vomiting, anorexia, and rash.[45] LOTUS (NCT02162719) is a randomized, double-blind, placebo-controlled international phase II study to evaluate the efficacy of ipatasertib combined with paclitaxel compared with placebo with paclitaxel in approximately 120 patients with previously untreated locally advanced or MBC.[46] The primary endpoint is PFS in all patients with TNBC and patients with TNBC with PTEN-low tumors. Randomization is 1:1 to either paclitaxel 80 mg/m^2 intravenously on days 1, 8, and 15 of each 28-day cycle and ipatasertib 400 mg orally daily on days 1 through 21 of each cycle or paclitaxel 80 mg/m^2 intravenously on days 1, 8, and 15 of each 28-day cycle and placebo. The trial is currently accruing.

The combination of weekly paclitaxel and ipatasertib is also being evaluated in the neoadjuvant setting. FAIRLANE (NCT02301988) is a randomized, double-blind, placebo-controlled, multicenter, preoperative phase II study designed to estimate the efficacy of ipatasertib combined with paclitaxel compared with placebo combined with paclitaxel in women with stage IA-IIIA (primary tumors ≥ 1.5 cm) TNBC.[47] The primary endpoint is pCR in the breast and lymph nodes. Approximately 150 patients will be enrolled at approximately 30 centers. Patients will be randomly assigned in a 1:1 ratio, stratified by the following three factors: PTEN status (null, low, medium), prior adjuvant/neoadjuvant treatment including chemotherapy with or without radiation, and disease-free interval from last dose of chemotherapy. Following surgical resection of primary tumor, patients are expected to continue postoperative treatment with a standard adjuvant anthracycline-based chemotherapy regimen. The trial is being conducted in collaboration with the SOLTI Breast Cancer Research Group and is ongoing.

OVEREXPRESSED GROWTH FACTORS IN TNBC

Several growth factor receptors are overexpressed in TNBC, including epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR). Phase II and III clinical trials with drugs that interrupt the EGFR and VEGFR signaling pathways have been conducted in breast cancer, but these approaches are no longer being pursued because of limited activity in an unselected TNBC population.[48-52] However, there still is promise in targeting other growth factor receptors, such as the FGFR.

Inhibition of the FGFR

FGFR signaling stimulates cell growth, survival, migration, and differentiation.[53] Approximately 9% of TNBC has *FGFR1* amplification, and approximately 4% of TNBC has amplification of the *FGFR2* gene.[9,54] Mutations in FGFR are less common in TNBC (< 1%).[55] Cell lines with *FGFR1* amplification or *FGFR2* or *FGFR4* mutations were sensitive to a FGFR inhibitor in cell line models.[54] Additionally, inhibition of FGFR in basal-like TNBC cell lines with *FGFR2* amplification led to decreased growth.[56] These data support the clinical investigation of FGFR inhibitors in TNBC, which may only benefit a very small subgroup. To date, there are several multitargeted kinase inhibitors in clinical development with relatively high potencies against FGFRs, and include dovitinib (TKI258), nintedanib (BIBF1120), ponatinib (AP24534), and lucitanib (CO-3810). Selective FGFR TKIs are AZD4547 and JNJ-42756493. Although no current study specifically targets the TNBC population, a phase II trial (NCT02202746) is ongoing in MBC evaluating oral lucitanib in tumors that have an FGFR1-amplification or 11q- amplification, and patients with TNBC are eligible.[57] A phase I trial is evaluating JNJ-42756493 in patients with solid tumors, and one cohort includes patients with breast cancer of any subtype as long as the tumors harbor an FGFR translocation or FGFR activating mutation (NCT01703481).[58] These trials with inclusion criteria more selective to specific FGFR alterations may prove more effective than previous trials treating unselected patients with breast cancer.

OTHER STRATEGIES

Other notable targets have led to additional clinical trial efforts to evaluate more tailored therapies for specific subpopulations within TNBC.

Blockade of the AR

Approximately 10% to 15% of TNBC express the AR.[59] The LAR subclass of TNBC is characterized by luminal gene expression and enriched for AR and AR gene targets.[20] This is the basis for targeting this subset of TNBC with antiandrogen therapy. In a multicenter phase II study by Gucalp et al, 150 mg of bicalutamide, an oral nonsteroidal antiandrogen, was administered daily to 26 patients with AR-positive, ER-negative, and PR-negative MBC, who were determined to be evaluable for the primary endpoint of clinical benefit rate (CBR; complete response + partial response + stable disease > 6 months).[60] A CBR of 18% (95% CI, 6% to 37%), consisting of all stable disease, and a median PFS of 12 weeks (95% CI, 11 to 22 weeks) was reported. The most common treatment-related toxicities were fatigue (21%), hot flashes (21%), limb edema (21%), aspartate aminotransferase elevation (25%), and alanine aminotransferase elevation (21%). Of note, 452 patients with ER-negative and PR-negative breast cancer were screened for AR expression, and 12% tested AR-positive, consistent with an earlier report.[59] The activity of a next-generation antiandrogen, enzalutamide, was evaluated in advanced AR-positive TNBC. In this multicenter trial, 26 patients evaluable for the primary endpoint of CBR (complete response + partial response + stable disease at 16 weeks) received enzalutamide 160 mg orally daily.[61] The

stage I result of this Simon 2-stage, phase II trial was a CBR of 42% (95% CI, 24% to 62%), including one complete response and one partial response. This met the prespecified efficacy endpoint. Study enrollment has been met and final results are expected to be reported later in 2015. In this prescreened sample of 404 patients, 55% of samples expressed AR—a much higher percentage than anticipated. Further analysis of the appropriate diagnostic to assess AR expression in tumor specimens is ongoing. Another androgen-directed therapy under evaluation in AR-positive TNBC is orteronel (TAK-700; NCT01990209), which is a nonsteroidal, androgen synthesis inhibitor that has been shown in preclinical studies to selectively inhibit the 17,20-lyase enzymes, critical to the production of androgens.[62] These studies show that AR is a promising and suitable therapeutic target in a small subset of TNBC, particularly the LAR subtype.

Inhibition of Notch Signaling with Gamma-Secretase Inhibitors

Research is beginning to show the potential of targeting the notch signal pathway as a possible treatment approach for patients with TNBC. The notch signaling pathway affects many cellular processes including proliferation, apoptosis, angiogenesis, and stem cell self-renewal.[63] The notch receptor is activated by the binding of membrane-bound ligand on a neighboring cell. This results in sequential cleavage by the ADAM17/TACE metalloprotease and gamma-secretase, leading to the release of the intracellular domain of notch (NICD). The NICD then translocates to the nucleus, activating downstream target genes, including *HES* and *HEY*.[64]

A preclinical study showed that TNBC xenograft models with *NOTCH1* rearrangements, retaining the gamma-secretase cleavage site, were associated with elevated levels of activated *NOTCH1* and have sensitivity to gamma-secretase inhibitors.[65] However, there were several rearrangements in *NOTCH2* that displayed constitutive signaling and were insensitive to gamma-secretase inhibition. In another study, 13% of TNBC were found to have PEST domain mutations in *NOTCH1*, *NOTCH2*, and *NOTCH3* receptors and patient-derived xenograft models that were highly sensitive to the gamma-secretase inhibitor, PF-03084014.[66] These mutations cause a truncation of the C-terminus of Notch removing the PEST domain, while retaining the gamma-secretase cleavage site. These data suggest that gamma-secretase inhibitors may have promise in treating a subset of TNBC with specific Notch alterations. A number of studies have investigated gamma-secretase inhibitors, such as R04929097 and MK-0752, in unselected metastatic TNBC. Several trials with the oral gamma-secretase inhibitor PF-03084014 are planned. A phase II trial (NCT02299635) will treat 48 patients with metastatic TNBC whose tumors harbor alterations in the NOTCH receptors with PF-03084014 at 150 mg orally twice daily.[67] The primary endpoint is overall response rate. A biomarker study (NCT02338531) will give PF-03084014 for 9 days at 150 mg on day 1 and day 9 and 150 mg twice daily on days 2 through 8 to patients with TNBC who have 1.5 cm of residual disease after neoadjuvant anthracycline and taxane-

based chemotherapy.[68] The primary endpoint of this trial is to assess HES4 gene expression level in tumor tissue samples before study drug and after 9 days of study drug to demonstrate that PF-03084014 is able to modulate the Notch pathway by down-regulating the expression of the tumor HES4 gene in chemoresistant TNBC.

Inhibition of the JAK2/STAT3 Pathway

Janus kinases (JAKs) are tyrosine kinases, and signal transducer and activation of transcription 3 (STAT3) proteins are major components of several cytokine receptor systems that regulate cell growth and survival.[69] Binding of the cytokine to the receptor induces dimerization, which activates the associated JAKs. The JAKs also phosphorylate STATs, which lead to their dimerization, nuclear translocation, and transcriptional regulation of genes that regulate cell differentiation, proliferation, and apoptosis. There is emerging preclinical evidence that disruption of the JAK2/STAT3 signaling could be an effective clinical strategy to treat TNBC. The IM subtype is also enriched with genes involved in immune cell signaling and cytokine signaling.[20] A preclinical study showed the JAK/STAT3 pathway was preferentially active in basal-like breast cancer cells, and inhibition of JAK2 resulted in reduced growth of xenografts.[70] Unlike myeloproliferative neoplasms, mutations in JAKs and STATs have not been well characterized. However, JAK2 amplifications were found more frequent in TNBC treated with neoadjuvant chemotherapy than in primary untreated basal-like breast tumors in the TCGA.[71] This observation may provide rationale to investigate JAK inhibitors in patients who have JAK2-amplified residual disease.

Ruxolitinib, a potent oral inhibitor of JAK1 and JAK2, is approved for the treatment of intermediate or high-risk myelofibrosis and is now being evaluated in breast cancer. A phase I trial (NCT02041429) is evaluating the combination of ruxolitinib given twice daily with weekly paclitaxel 80 mg/m^2, 3 weeks out of 4 weeks, in patients with MBC.[72] Once a recommended phase II dose is determined, the study will treat patients with triple-negative inflammatory breast cancer with ruxolitinib orally twice daily for 21 days in a 28-day cycle and weekly paclitaxel for 12 weeks followed by dose-dense AC for four cycles. The primary endpoint is biologic, and the trial will evaluate expression of pSTAT3 in triple-negative inflammatory breast cancer tumors before and after treatment, with an expected decrease in pSTAT3 expression post-therapy.

Targeting Trop-2

Trop-2, also referred to as M1S1, TACSTD2, EGP-1, is a cell surface protein overexpressed in several epithelial cancers, but not in corresponding normal tissues.[73] Trop-2 is a transmembrane calcium signal transducer and is involved in the regulation of cell-cell adhesion.[74] Membrane-associated Trop-2 was found to be associated with poor prognosis in breast cancer.[75] There is a growing interest in targeting Trop-2 in TNBC. IMMU-132 (isactuzumab govitecan) is an antibody-drug conjugate containing the humanized mono-

clonal antibody, hRS7, against Trop-2, which is linked to the active metabolite of irinotecan, 7-ethyl-10-hydroxycamptothecin (SN-38). The antibody moiety of IMMU-132 selectively binds to Trop-2. After internalization and proteolytic cleavage, SN-38 is delivered preferentially to the tumor cells. Preclinical data shows that IMMU-132 resulted in increased tumor regression in MDA-MD-468 TNBC xenograft models, compared to irinotecan or to the antibody-drug conjugate control.[76] IMMU-132 received Fast Track designation in January 2015 from the FDA for treatment of patients with TNBC who have progressed on prior therapies for metastatic disease. A phase I/II trial of IMMU-132 was conducted in advanced epithelial cancers, including TNBC. There was no prescreening for Trop-2 expression. The recommended phase II dose of IMMU-132 was 10 mg/kg intravenously on days 1 and 8 of a 21-day cycle. The toxicity was mostly neutropenia, and diarrhea was low grade.[76] An expansion cohort enrolled 23 patients with pretreated metastatic TNBC (prior number of median regimens was 4) with a response rate of 30% consisting of 7 partial responses, and a CBR (partial response + stable disease > 6 months) of 40%.[77] Immunohistochemical data on Trop-2 scoring is being collected. A phase II trial will treat 80 patients with metastatic TNBC who have received two or more prior regimens with IMMU-132 alone or in combination with carboplatin (NCT02161679).[78] Further research is necessary to evaluate the strategy of using antitrop-2 therapeutics for breast cancer and the relationship of Trop-2 expression to response.

CONCLUSION

TNBC is a heterogeneous disease. The identification of several specific subtypes characterized by different biologic pathways and various sensitivities to chemotherapy is instrumental in delivering more personalized therapy for TNBC. Ongoing and future clinical research in selected subsets of TNBC will validate the efficacy of such novel treatment strategies.

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BREAST CANCER

Optimizing Treatment of HER2-Positive Breast Cancer

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Neoadjuvant and Adjuvant Therapy for HER2 Positive Disease

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OVERVIEW

Since the initial description of the HER2 proto-oncogene as a poor prognostic factor in breast cancer in 1987, to the first randomized trial of a monoclonal antibody directed against HER2 in combination with chemotherapy for the treatment of metastatic HER2-positive breast cancer published in 2001, to the American Society of Clinical Oncology (ASCO) 2005 Annual Meeting in which we saw the unprecedented collective presentations demonstrating the dramatic benefit of trastuzumab in the adjuvant setting—the clinical landscape of HER2-overexpressing breast cancer has forever changed. More recently, there has been increasing use of preoperative chemotherapy and anti-HER2 targeted therapies in primary operable HER2 disease in the research domain and in clinical practice. In the next few years, we will see if dual adjuvant anti-HER2 antibody inhibition produces clinically significant improvements in outcome; understand if there is a role of small molecule inhibitors of the HER family of receptors either in combination or sequential to trastuzumab; further refine the relationship between pathologic complete response (pCR) and long-term clinical outcomes; and find predictive biomarkers to identify cohorts of patients that may need differential combinations and/or durations of anti-HER2 therapies.

From the original description of the human epidermal growth factor receptor 2 (HER2) as a proto-oncogene, to being a prognostic marker, to then being a therapeutic target has revolutionized the categorization, risk assessment, and treatment of breast cancer. Though this subtype of breast cancer represents less than 25% of incident breast cancers, many lessons can be learned from the development of anti-HER2 therapies in early-stage disease. In particular, much work has recently been put forth in neoadjuvant trials assessing combinations of anti-HER2 therapies. This review will touch on the landmark studies in both the adjuvant and neoadjuvant settings and comment on some of the controversies that still remain today in both clinical care and as research questions.

LANDMARK RANDOMIZED TRIALS OF ADJUVANT TRASTUZUMAB

Current clinical guidelines clearly state that standard of care in 2015 recommends the use of the monoclonal anti-HER2 antibody trastuzumab in combination with or after adjuvant chemotherapy in medically fit patients diagnosed with stage I to III HER2-positive breast cancer.[1,2] The four landmark randomized trials investigating the benefit of adjuvant trastuzumab (National Surgical Adjuvant Breast and Bowel Project [NSABP] B-31, North Central Cancer Treatment Group [NCCTG] N9831, HERA, and Breast Cancer International Research Group [BCIRG] 006) in their initial analysis reported outcomes with median follow-ups of 24 to 36 months.[3-5] The range in benefit in disease-free survival (DFS) in favor of trastuzumab was with hazard ratios (HRs) between 0.48 and 0.67 (p < 0.0001), and the range in benefit in overall survival (OS) was between 0.59 and 0.67 (p = NS to p = 0.015). Absolute improvements in DFS ranged from 6% to 11%, with corresponding absolute differences in OS of 1% to 2.5% (Table 1).

With longer follow-up from these trials (now 8-year median follow-up from HERA and from the combined analyses of NSABP B-31 and NCCTG N9831), there continues to be statistically and clinically significant improvements in DFS and OS.[6-8] Though the magnitude of benefit, as measured by HRs, appears to have lessened slightly over time as more events (both relapses and deaths) occur, absolute gains in overall survival are larger now than in earlier analyses (Table 2). The selective crossover of some of the patients initially randomly assigned to the no trastuzumab arm across the trials will have mitigated some of the initial differences seen in the studies. However, relapses unfortunately continue to occur at a relatively constant rate over time in the trastuzumab-treated arm(s)—with an estimated 10-year DFS of 73.7% from the combined analyses of NSABP B-31 and NCCTG N9831.[6] What is encouraging, however, is that with longer follow-up, the cumulative incidence of cardiac adverse events plateaus, with cardiac events rarely occurring following completion of trastuzumab treatment.[7] In the HERA study, at 8-years follow-up, only 4.1% of patients experienced

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Disclosures of potential conflicts of interest are found at the end of this article.

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TABLE 1. Initial Reports from the Large Adjuvant Trastuzumab Trials

Trial	Trastuzumab Duration	Median Follow-up (Months)	Treatment Arms	No. of Patients	HR for DFS (95% CI)	2-3 yr DFS	HR for OS (95% CI)	2-yr OS
HERA[4]	1 yr	24	Chemotherapy	1,698		77.4%		95.1%
			Chemotherapy →H	1,703	0.64 (0.54-0.76)	85.8%	0.66 (0.47-0.91)	96.0%
NSABP B-31[3]	1 yr	24	AC →P	1,679		75.4%		91.7%
NCCTG N9831			AC →P →H	1,672	0.48 (0.39-0.59)	87.1%	0.67 (0.48-0.93)	94.3%
BCIRG 006[5]	1 yr	36	AC →T	1,073		81%		N/A
			AC →TH	1,074	0.61 (0.48-0.76)	88%	0.59 (0.42-0.85)	N/A
			TcarboH	1,075	0.67 (0.54-0.83)	87%	0.66 (0.47-0.93)	N/A

Abbreviations: HR, hazard ratio; DFS, disease-free survival; OS, overall survival; H, trastuzumab; NSABP, National Surgical Adjuvant Breast and Bowel Project; A, doxorubicin; C, cyclophosphamide; P, paclitaxel; NCCTG, National Central Cancer Treatment Group; BCIRG, Breast Cancer International Research Group; T, docetaxel; carbo, carboplatin.

New York Heart Association class I or class II cardiac dysfunction with a left ventricular ejection fraction (LVEF) drop of 10% or more below baseline and to an absolute LVEF of 50% or less. Furthermore, it is felt that the majority of cardiac events secondary to trastuzumab are reversible in nature.

Perhaps the remaining limited questions at hand specific to clinical practice in relation to these landmark trials are (1) treatment of HER2-positive $T1_{a-b}N_0$ breast cancers, (2) anthracycline or no anthracycline-based regimen, and (3) concurrent compared with sequential trastuzumab therapy. A small minority of patients in these four pivotal trials had $T1_{a-b}N_0$ breast cancers. Several retrospective prognostic studies demonstrate a significantly worse prognosis in HER2-positive $T1_{a-b}N_0$ breast cancers compared with HER2-negative $T1_{a-b}N_0$ breast cancers.[9,10] In a recent analysis from the National Comprehensive Cancer Network (NCCN) database examining this exact question, 4,113 patients with $T1_{a-b}N_0$ breast cancers treated between 2000 and 2009 were assessed by biologic subtype and receipt of chemotherapy (or not) and trastuzumab (or not).[11] Within this subgroup not treated

with chemotherapy or trastuzumab, the 5-year distant relapse-free survival (DRFS) ranged between 93% and 96%. The rates of invasive DFS (IDFS), however, was lower, particularly in $T1_{a-b}N_0$ hormone receptor–negative/HER2-positive breast cancers, with an estimated 5-year IDFS of 68%. Thus, the summation of most studies would suggest considering adjuvant chemotherapy and trastuzumab in $T1_bN_0$ HER2-positive (regardless of hormone receptor status) breast cancers in medically fit patients without high competing risks of mortality. However, for $T1_aN_0$ HER2-positive breast cancer, the risks and inconvenience of treatment may potentially outweigh the benefit of therapy—especially for hormone receptor–positive/HER2-positive $T1_aN_0$ breast cancers.

In the same vein, the selection of adjuvant chemotherapy regimen in combination with trastuzumab varies. Based on the risk/benefit ratio, consideration should be made for a limited nonanthracycline-based regimen in stage I disease. Though not studied within a randomized trial, the regimens of weekly paclitaxel (80 mg/m^2 weekly for 12 weeks) concurrent with trastuzumab (for 1 year) or four cycles of docetaxel and cyclophosphamide (75 mg/m^2 and 600 mg/m^2, respectively) every 3 weeks for four cycles concurrent with trastuzumab (for 1 year) both demonstrate a generally low toxicity profile with very favorable clinical outcomes.[12,13] In the recently published phase II study of 406 women with primarily stage I HER2-positive disease (> 90%), the 3-year IDFS was 98.7% with weekly paclitaxel for 12 weeks concurrent with trastuzumab.[12] There was a reported 0.5% rate of symptomatic congestive heart failure and a 3.2% rate of asymptomatic declines in LVEF. Likewise, in the phase II single-arm, open-label study of docetaxel and cyclophosphamide (four cycles) concurrent with trastuzumab, the reported 2-year DFS of 97.8% was quite favorable as well. Otherwise, for stage II to III disease, consideration should be given for the regimens studied in the landmark pivotal trials, the vast majority of which contained an anthracycline (four cycles) sequentially followed by a taxane (four cycles), except for the six cycles of docetaxel, carboplatin, and trastuzumab arm in BCIRG 006.[5]

Lastly, it would seem both practical and potentially more efficacious to deliver the trastuzumab concurrent with the

KEY POINTS

- The treatment of HER2-positive early-stage breast cancer should incorporate 12 months of adjuvant trastuzumab, preferably concurrent with a taxane backbone.
- Neoadjuvant systemic therapies are now routinely delivered in both primary operable and locally advanced breast cancer in the research domain and in clinical practice.
- The combination of lapatinib and trastuzumab inconsistently improved pathologic complete response (pCR) rates across its neoadjuvant trials and ultimately did not improve disease-free survival (DFS) in the large adjuvant ALTTO trial.
- In a large pooled analysis, pCR (with or without the presence of in situ disease) in the breast and nodes most closely correlates with DFS and overall survival.
- Well-designed, randomized, neoadjuvant trials with tissue acquisition are essential to more precisely plan adjuvant trials, assess for predictive biomarkers, and accelerate drug development for early-stage disease.

TABLE 2. Longer-Term Follow-up from the Large Adjuvant Trastuzumab Trials

Trial	Median Follow-up (Years)	Treatment Arms	HR for DFS (95% CI)	DFS	HR for OS (95% CI)	OS
HERA[7]	8 yr	Chemotherapy		76.0%		N/A
		Chemotherapy → H	0.76 (0.67-0.86)		0.76 (0.65-0.88)	N/A
NSABP B-31[6]	8.4 yr	AC → P		62.2%		75.2%
NCCTG N9831		AC → P → H	0.60 (0.53-0.68)	73.7%	0.63 (0.54-0.73)	84.0%
BCIRG 006[8]	5.5 yr	AC → T		75%		87%
		AC → TH	0.64 (0.53-0.78)	84%	0.63 (0.48-0.81)	92%
		TCarboH	0.75 (0.63-0.90)	81%	0.77 (0.60-0.99)	91%

Abbreviations: HR, hazard ratio; DFS, disease-free survival; OS, overall survival; H, trastuzumab; NSABP, National Surgical Adjuvant Breast and Bowel Project; A, doxorubicin; C, cyclophosphamide; P, paclitaxel; NCCTG, National Central Cancer Treatment Group; BCIRG, Breast Cancer International Research Group; T, docetaxel; carbo, carboplatin.

taxane. In the NCCTG N9831 study, one arm delivered paclitaxel (weekly) concurrent with trastuzumab (arm C), whereas in another arm, the trastuzumab was delivered sequential (arm B).[14] Alhtough there was a numerical increase in DFS in favor of the concurrent arm (84.4% vs. 80.1%), it did not meet statistical significance based on the interim analysis criteria (arm C/arm B HR 0.77; 95% CI, 0.53 to 1.11). However, as there was no difference in toxicity between these two arms, and for convenience and earlier completion of therapy, it would be overall advantageous to deliver the trastuzumab concurrent with the taxane.

LANDMARK RANDOMIZED TRIALS OF NEOADJUVANT HER2-TARGETED THERAPIES

The standard clinical use of neoadjuvant chemotherapy today can be categorized into two populations of patients: the locally advanced breast cancers (LABC) and the primary operable breast cancers (POBC). The defined purpose for the use of neoadjuvant chemotherapy for LABC is to convert a baseline inoperable condition to an operable state. Whereas in POBC, the standard clinical utility of neoadjuvant chemotherapy has the potential to downstage a tumor and thus convert a baseline mastectomy candidate into a breast-conservation candidate. However, as individual trials and the Early Breast Cancer Trialists Collaborative Group overview of neoadjuvant trials demonstrated that standard chemotherapy regimens (anthracyclines ± taxanes) whether given preoperatively or postoperatively (adjuvant) provided the same long-term clinical outcomes, one can now potentially deliver standard systemic treatment in either the neoadjuvant or adjuvant setting with similar confidence.[15] The same holds true, if not even more so, for HER2-positive breast cancers. The additional advantages of delivery in the neoadjuvant setting include the ability to study new agents with the utility of a surrogate endpoint for outcome; the ability to obtain tumor tissue for pharmacodynamic assessment, understanding of biology and discovery of predictive biomarkers; earlier initiation of systemic therapies; and the ability to monitor response (which is clearly not possible in the adjuvant setting).

The first landmark trial investigating the benefit of neoadjuvant trastuzumab in the LABC setting was the NOAH trial.[16] NOAH randomly selected 228 patients with HER2-positive disease to receive a neoadjuvant regimen consisting of doxorubicin, paclitaxel, cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) with or without concurrent trastuzumab (throughout the entire chemotherapeutic regimen). This is the largest randomized trial of a true locally advanced and inflammatory population to date. The trastuzumab-treated cohort demonstrated a significantly superior rate of pCR in breast and nodes (total pCR [tpCR]; 38% vs. 19%; p = 0.001), which ultimately translated to an improved 3-year event-free survival (EFS; 71% vs. 56%, HR 0.59; 95% CI, 0.38 to 0.90).[17] Not only was a doubling of the tpCR rate impressive, but also the magnitude of improvement in EFS of a similar degree (HR 0.59) as the landmark adjuvant trastuzumab trials is an interesting observation. Although the use of the specific chemotherapy regimen from NOAH is not likely to be common, the concept of neoadjuvant trastuzumab concurrent with chemotherapy now is.

Lapatinib-Based Neoadjuvant Trials

Lapatinib is a small molecule tyrosine kinase inhibitor (TKI) of the HER1 and HER2 receptors. Despite the lack of a head-to-head trial with trastuzumab in the metastatic setting, several randomized neoadjuvant trials were initiated. All these trials included both POBC and HER2-positive LABC. The GeparQuinto study compared trastuzumab (8 mg/kg loading dose followed by 6 mg/kg every 3 weeks given concurrently with chemotherapy during the preoperative period) with lapatinib (1,250 mg/day continuously for 12 weeks) added to a backbone of four cycles of epirubicin (90 mg/m^2) and cyclophosphamide (600 mg/m^2) followed by four of docetaxel (100 mg/m^2) in 615 patients with HER2-positive disease.[17] A significantly higher tpCR rate (breasts and nodes) was seen in the trastuzumab arm (30.3% vs. 22.7%; odds ratio 0.68; 95% CI, 0.47 to 0.97; p = 0.04). Furthermore, in this study, dose reductions were required in nearly one-third of patients receiving lapatinib, prompting a protocol amendment reducing the lapatinib dose to 1,000 mg/m^2.

The smaller CHER-LOB study was conducted using a chemotherapy backbone of weekly paclitaxel (80 mg/m^2) for 12 weeks followed by three-weekly 5-fluorouracil, epirubicin, cyclophosphamide (FEC; 500/75/500 mg/m^2, respectively)

with either weekly trastuzumab (4 mg/kg loading dose followed by 2 mg/kg weekly) or lapatinib (1,250 mg daily) given concurrently with chemotherapy.[18] This study also examined the efficacy of a trastuzumab-lapatinib doublet with dose-adjusted lapatinib (750 mg/day). Dual HER2 targeting substantially improved pCR (breast and nodes) over either trastuzumab or lapatinib alone. pCR rates were 46% (90% CI, 34.4% to 58.9%), 25% (90% CI, 13.1% to 36.9%), and 26.3% (90% CI, 14.5% to 38.1%), respectively. As was seen in the GeparQuinto trial, gastrointestinal toxicity with lapatinib was a significant adverse event. More than 50% of those receiving lapatinib experienced diarrhea of grade 1 or higher, even after a protocol amendment directing a dose reduction from 1,500 mg/day to 1,250 mg/day in the single-agent arm, and from 1,000 mg/day to 750 mg/day in the doublet arm.

The NeoAdjuvant Lapatinib and/or Trastuzumab Optimization (NeoALTTO) trial was a three-armed study addressing the comparative efficacy of single compared with dual HER2 blockade using trastuzumab (4 mg/kg loading dose followed by 2 mg/kg weekly), lapatinib (1,500 mg daily), or a combination (trastuzumab standard dose and lapatinib 1,000 mg daily), alongside weekly paclitaxel (80 mg/m^2) chemotherapy.[19] This trial scheduled a 6-week lead in period of targeted therapy alone before introduction of paclitaxel for a further 12 weeks of therapy. Dual HER2 targeting induced tpCR (breast and nodes) rates in 46.8% of patients compared

with 27.6% in the trastuzumab alone arm (p = 0.0007). There was no statistically significant difference in pCR rates between the trastuzumab alone and lapatinib alone arms (27.6% and 20%; p = 0.13).

In a fourth trial, the NSABP B-41 study randomly selected 529 patients with HER2-positive disease to receive doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 3 weeks for four cycles, followed by weekly paclitaxel (80 mg/m^2) for a further 12 weeks with either concurrent weekly trastuzumab (4 mg/kg loading dose followed by 2 mg/kg weekly), 1,250 mg of lapatinib daily, or weekly trastuzumab plus lapatinib (750 mg/day).[20] pCR was achieved for 62% of patients receiving combination HER2 targeting compared with 52.5% in the trastuzumab arm (p = 0.095). There was no significant difference between the trastuzumab and lapatinib alone arms (52.5% vs. 53.2%; p = 0.990).

Lastly, the Cancer and Leukemia Group B 40601, a neoadjuvant phase III trial of weekly paclitaxel (T) and trastuzumab (H) with and without lapatinib (L) in HER2-positive breast cancer, was presented at the 2013 ASCO Annual Meeting.[21] This trial randomly selected 305 patients, of which two-thirds had clinical stage II disease. The pCR rates in the breast alone were 51% (42% to 60%) THL, 40% (32% to 49%) TH, 32% (22% to 44%) TL. The combination arm of THL was not significantly different from the standard arm of trastuzumab and paclitaxel (p = 0.11; Table 3).

TABLE 3. Neoadjuvant Trials of Dual HER2 Targeted Therapies

Trial	No. of Patients	Treatment Arms	pCR (Breast and Nodes)	p	3-yr EFS
GeparQuinto[17]	309	ECH → TH	31.3%	p < 0.05	N/A
	311	ECL → TL	21.7%		N/A
NeoALTTO[19]	149	H → HP	27.6%		76%
	154	L → LP	20.0%	p = 0.13	78%
	152	HL → HLP	46.9%	p = 0.001	84%
CHER-LOB[18]	36	HP → FECH	25%		N/A
	39	LP → FECL	26.3%		N/A
	46	HLP → FECHL	46.7%		N/A
NSABP B-41[20]	177	AC → HP	52.5% (breast)		N/A
	171	AC → LP	53.2% (breast)	p = 0.9852	N/A
	171	AC → HLP	62.0% (breast)	p = 0.095	N/A
CALGB 40601[21]	120	HP	40% (breast)		N/A
	67	LP	32% (breast)		N/A
	118	HLP	51% (breast)	p = 0.11	N/A
NeoSphere[22]	107	TH	29.0% (breast)		N/A
	107	PerHT	45.8% (breast)	p = 0.0141	N/A
	107	PerH	24.0% (breast)		N/A
	96	PerT	16.8% (breast)		N/A
TRYPHENA[23]	73	PerHFEC → PerTH	61.6% (breast)		N/A
	75	FEC → PerTH	57.3% (breast)		N/A
	77	TcarboHPer	66.2% (breast)		N/A

Abbreviations: pCR, pathologic complete response; EFS, event-free survival; E, epirubicin; C, cyclophosphamide; H, trastuzumab; T, docetaxel; L, lapatinib; P, paclitaxel; F, 5-fluorouracil; NSABP, National Surgical Adjuvant Breast and Bowel Project; A, doxorubicin; CALGB, Cancer and Leukemia Group B; Per, pertuzumab; carbo, carboplatin.

Pertuzmab-Based Neoadjuvant Trials

Pertuzumab, a humanized monoclonal antibody that inhibits dimerization of HER2 with other HER receptors, has been evaluated in two randomized phase II studies. In the NeoSphere trial, 417 women with HER2-positive POBC/LABC disease were randomly selected to receive either four cycles of neoadjuvant trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks), docetaxel (75 mg/m^2 escalating to 100 mg/m^2 as tolerated) and pertuzumab (loading dose 840 mg, followed by 420 mg every 3 weeks), or trastuzumab plus docetaxel, or pertuzumab and trastuzumab without chemotherapy, or pertuzumab plus docetaxel.[22] The combination of dual HER2 targeting and docetaxel induced a pCR (breast) for 45.8% (95% CI, 36.1 to 55.7) compared with 29% of those randomly assigned to trastuzumab and docetaxel (95% CI, 20.6 to 38.5; p = 0.0141). After surgery, all patients received three cycles of FEC and the remainder of 1 year of trastuzumab. pCR was achieved for 24.0% of those receiving pertuzumab and docetaxel and 16.8% of women who were treated with dual HER2 targeted therapy in the absence of chemotherapy. Neither short- nor long-term clinical outcomes (EFS and OS) have been reported yet from NeoSphere.

TRYPHENA was a phase II trial with cardiac safety as the primary endpoint.[23] All 225 participants received dual HER2 targeting with trastuzumab and pertuzumab. The three study arms were randomly assigned to 500 mg 5-fluorouracil, 100 mg epirubicin, and 500 mg/m^2 cyclophosphamide (FEC100) for three cycles, followed by docetaxel (75 mg/m^2) with concurrent with trastuzumab and pertuzumab; FEC for three cycles followed by docetaxel with trastuzumab and pertuzumab given only alongside docetaxel; or six cycles of docetaxel, carboplatin, trastuzumab, and pertuzumab. In this trial, pCR (breast) was a secondary endpoint, with rates ranging between 57.3% and 66.2%, in keeping with results seen elsewhere. The lack of an arm without pertuzumab limits the extrapolation of these results to other studies and to standard clinical practice.

On September 30, 2013, the U.S. Food and Drug Administration (FDA) granted accelerated approval to pertuzumab in combination with trastuzumab and chemotherapy as a neoadjuvant treatment regimen in patients with HER2-positive locally advanced, inflammatory, or early-stage disease (tumor size > 2 cm or with positive lymph nodes).[24] This was a landmark ruling as pertuzumab is the first FDA-approved agent for use in the neoadjuvant setting. The allowance of use in clinical care and guidelines (NCCN[2]) does provide a window of opportunity to potentially prevent relapses in higher-risk cohorts while awaiting results from the confirmatory adjuvant trial (APHINITY). Not only is this of potential benefit to patients today, but it also excites the drug development world about an accelerated path to drug approval in the much larger cohort of early-stage disease.

AREAS OF ONGOING CONTROVERSY

Despite the breadth of the trials and the consistency of results across them, a number of questions remain regarding the op-

timal use of anti-HER2 targeted therapy in early-stage disease. We eagerly wait to see if dual adjuvant anti-HER2 antibody inhibition with trastuzumab and pertuzumab produces clinically significant improvements in outcome. Results from both the metastatic setting and the neoadjuvant trials (in particular NeoSphere) would predict that the large adjuvant trial APHINITY (NCT01358877) will likely be significant. The question will then be how significant will the result need to be to alter standard clinical practice and be cost-effective. The following are other remaining questions.

Duration of Adjuvant Trastuzumab

At present the standard of care is for 1 year of adjuvant trastuzumab therapy. In the HERA study, 2 years of trastuzumab did not produce any additional benefit compared with 1 year of trastuzumab, but it did increase the secondary cardiac event rate.[7] The PHARE study was a noninferiority study comparing 6 months of trastuzumab to 12 months of trastuzumab sequential to at least four cycles of adjuvant chemotherapy.[25] A total of 3,384 patients were randomly selected, with a median of 42.5 months of follow-up at time of reporting. Two-year DFS was 93.8% in the 12-month group and 91.1% in the 6-month group (HR 1.28; 95% CI, 1.05 to 1.56; p = 0.29). The trial did not meet its noninferiority endpoint, solidifying 12 months of trastuzumab therapy as the current standard of care, until other clinical trials comparing 6 months to 12 months of trastuzumab therapy (PERSEPHONE, NCT00615602) report.

The FinHER study was a phase III, randomized adjuvant trial of 1,010 women, of which 232 had HER2-amplified tumors.[26] In the HER2-positive cohort, patients randomly assigned to 9 weeks of trastuzumab or not concurrent with three cycles of docetaxel or vinorelbine followed in all groups with three cycles of FEC (600 mg, 60 mg, 600 mg/m^2, respectively). The 3-year RFS was significantly greater in the trastuzumab-treated cohort (HR 0.42; 95% CI, 0.21 to 0.83: p = 0.01) versus no trastuzumab. However, because this is a small study relative to the landmark adjuvant trastuzumab trials, and the chemotherapy regimen is not standard (including the lower dose of FEC), we await the results from the confirmatory phase III trials—SOLD and Short-HER—before considering 9 weeks of trastuzumab therapy as standard of care.

Role of HER2-Targeted Tyrosine Kinase Inhibitors

Potent small molecule TKI inhibitors exist, both reversible and irreversible, that block some members (e.g., lapatinib reversibly blocks primarily HER1 and HER2) or all members (e.g., neratinib irreversibly blocks HER1 to HER4) of the HER family of transmembrane receptors. The neoadjuvant trials (as discussed above) with lapatinib failed to demonstrate greater efficacy of lapatinib as monotherapy compared to standard trastuzumab. The combination of lapatinib and trastuzumab inconsistently demonstrates a higher pCR rate, although with a need to dose reduce lapatinib because of gastrointestinal toxicity. The NeoALTTO trial has recently reported at 3.8 years of follow-up, and although a numerical

trend was seen, there was no significant difference in EFS between the combination arm and the trastuzumab arm (HR 0.78; 95% CI, 0.47 to 1.28; p = 0.33).[27]

The ALTTO trial randomly assigned 8,381 patients, of whom 40% had node-negative disease and 57% had hormone receptor–positive disease.[28] The four arms of the study were trastuzumab for 12 months (T), lapatinib for 12 months (L), trastuzumab for 12 weeks followed sequentially by lapatinib for 34 weeks (T→L), and the combination of trastuzumab and lapatinib for 12 months (TL). Although the study was powered for 850 DFS events, the study was analyzed at 4.5 years (median) of follow-up as per protocol stipulation but with only 555 DFS events. At the first efficacy interim analysis, the comparison of L to T crossed the futility boundary, and as such, the L arm was crossed over to a recommended course of trastuzumab for 12 months. At the time of reporting of the efficacy of the primary endpoint at the 2014 ASCO Annual Meeting, the 4-year DFS for the T, T→L, and TL arms were 86%, 87%, and 88%, respectively. The HR comparing TL and T was 0.84 (0.70–1.02; p = 0.048), which was not significant, for a p ≤ 0.025 was required for statistical significance. The interaction test for hormone receptor status and for schedule of anti-HER2 therapy was not significant. However, numerically, the sequential administration of anti-HER2 therapy arms had some difference (T vs. TL 4-year DFS of 83% vs. 86%, respectively), whereas the combination arms did not (T vs. TL 4-year DFS of 90% vs. 90%, respectively). Lapatinib was also associated with a greater rate of adverse events, which subsequently led to only 60% to 78% of patients in the lapatinib treatment arms receiving at least 85% of the intended dose intensity of L. These factors, in addition to a time-driven analysis (rather than the initial powering of the study for an event-driven analysis) may have affected the true efficacy of the dual anti-HER2 combination arm.

Neratinib has been studied in a neoadjuvant manner as part of the I-SPY 2 program, as well as in an extended manner in a placebo-controlled trial in a population of patients following 1 year of standard adjuvant trastuzumab-based therapy. In the I-SPY 2 trial, neratinib was given in combination with weekly paclitaxel (80 mg/m² for 12 weeks) in both the HER2-positive and HER2-negative cohorts.[29] All patients subsequently received sequential doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) for four cycles without neratinib or trastuzumab before proceeding to definitive surgery. In the HER2-positive signature cohort, the pCR rate was 39% in the neratinib plus paclitaxel arm, compared to 23% in the trastuzumab plus paclitaxel arm. The magnitude of improvement in pCR was similar regardless of the hormone receptor status in the HER2-positive cohort. No significant difference in pCR rates was seen in the HER2-negative signature cohort. A significant rate of grade 2–3 diarrhea was seen, however, in the neratinib arms resulting in dose reductions/holds in 65% of cases for neratinib (vs. 15% in the control arm).

ExteNET is a double-blind phase III trial of neratinib (240 mg orally once daily) versus placebo in 2,821 women with early-stage HER2-positive (local confirmation) breast cancer after adjuvant treatment with trastuzumab. The primary endpoint of the study was DFS. The results of the study have not yet been presented in a peer review forum, but a press release from July 22, 2014, stated, "The results of the trial demonstrated that treatment with neratinib resulted in a 33% improvement in disease free survival versus placebo. The hazard ratio was determined to be 0.67, which was statistically significant with a p value of 0.0046. The secondary endpoint of the trial was disease free survival including ductal carcinoma in situ (DFS-DCIS). The results of the trial demonstrated that treatment with neratinib resulted in a 37% improvement in disease free survival including ductal carcinoma in situ versus placebo. The hazard ratio was determined to be 0.63, which was statistically significant with a p value of 0.0009."[30] Results from this potential practice-changing trial are expected to be presented at the 2015 ASCO Annual Meeting as we await the details of the absolute improvements in DFS and other clinical endpoints as well as the associated toxicities on trial.

Correlation of pCR and Long-Term Clinical Outcomes

There remains an ongoing debate regarding the correlation of pCR status and long-term clinical outcomes such as DFS, EFS, and OS. The attractiveness of an early surrogate marker of efficacy in early-stage disease allows for the use of the neoadjuvant space to test new drugs for efficacy (and toxicity) to expedite development and approval of new therapies in early-stage disease. Multiple studies have repeatedly demonstrated a prognostic effect for the cohort of patients achieving a pCR—particularly those achieving a pCR in breast and lymph nodes (tpCR). Recently, a pooled analysis of 12 large trials of 11,955 patients treated with preoperative chemotherapy with available data on pCR and at least 3-year follow-up data on EFS and OS was performed by the FDA (CTNeoBC pooled analysis).[31] The analysis concluded several points. First, the definition of eradication of tumor in breast and lymph nodes, with or without presence of in situ disease (ypT0/is ypN0) was most closely associated with improved EFS (0.48; 95% CI, 0.43 to 0.54) and OS (HR 0.36; 95% CI, 0.31 to 0.42). Moving forward this should be the consistent and standard definition used as the primary endpoint in neoadjuvant trials. Second, the association between pCR and long-term outcomes was strongest in triple-negative breast cancer and HER2-positive/estrogen receptor–negative breast cancers treated with trastuzumab. Last, in their analysis, they found little association between the degree of increase in pCR response and EFS. The German Breast Group performed a similar analysis with seven of their trials involving 6,366 patients.[32] These patients were also included in the CTNeoBC pooled analysis. Their overall conclusions were similar to the FDA analysis but with some slight differing results. They found that no invasive and no in situ disease in breast and nodes (ypT0ypN0) was the greatest discriminator with long-term outcome. They also concluded that pCR was perhaps not a suitable surrogate endpoint for hormone receptor–positive/HER2-positive breast cancer.

CONCLUSION

In conclusion, in the post-adjuvant trastuzumab era, the outcome of HER2-positive breast cancer has now evolved from a subtype with the worse prognosis to one with arguably the best long-term outcomes. Current standard of care should incorporate 12 months of adjuvant trastuzumab and preferably be concurrent with a taxane backbone. Moving forward we must continue embracing the neoadjuvant model as both standard of care and an important strategy to test new therapeutic agents and accelerate drug development. Well-designed, randomized, neoadjuvant studies importantly allow us to more intelligently guide and support the trial design of adjuvant studies and, by doing so, will minimize overall timelines for drug development in early-stage disease. Although an adequate signal from preoperative trials may not necessarily predict the outcome in a confirmatory adjuvant trial, the lack of a signal should halt further development in a more resource-intensive adjuvant trial.

Disclosures of Potential Conflicts of Interest

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CANCER PREVENTION, GENETICS, AND EPIDEMIOLOGY

Breast Cancer Chemoprevention: Proven but Publicly Ignored—An Update of Benefit and Risk Data

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Addressing Barriers to Uptake of Breast Cancer Chemoprevention for Patients and Providers

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OVERVIEW

Breast cancer is the most common malignancy among women in the United States, and the primary prevention of this disease is a major public health issue. Because there are relatively few modifiable breast cancer risk factors, pharmacologic interventions with antiestrogens have the potential to significantly affect the primary prevention setting. Breast cancer chemoprevention with selective estrogen receptor modulators (SERMs) tamoxifen and raloxifene, and with aromatase inhibitors (AIs) exemestane and anastrozole, is underutilized despite several randomized controlled trials demonstrating up to a 50% to 65% relative risk reduction in breast cancer incidence among women at high risk. An estimated 10 million women in the United States meet high-risk criteria for breast cancer and are potentially eligible for chemoprevention, but less than 5% of women at high risk who are offered antiestrogens for primary prevention agree to take it. Reasons for low chemoprevention uptake include lack of routine breast cancer risk assessment in primary care, inadequate time for counseling, insufficient knowledge about antiestrogens among patients and providers, and concerns about side effects. Interventions designed to increase chemoprevention uptake, such as decision aids and incorporating breast cancer risk assessment into clinical practice, have met with limited success. Clinicians can help women make informed decisions about chemoprevention by effectively communicating breast cancer risk and enhancing knowledge about the risks and benefits of antiestrogens. Widespread adoption of chemoprevention will require a major paradigm shift in clinical practice for primary care providers (PCPs). However, enhancing uptake and adherence to breast cancer chemoprevention holds promise for reducing the public health burden of this disease.

Unlike cardiovascular disease, limited pharmacologic options exist for the primary prevention of cancer. Antiestrogens, such as SERMs and AIs, have been shown to reduce breast cancer incidence by up to 50% to 65% among women at high risk.[1-5] Based on this evidence, the U.S. Preventive Services Task Force (USPSTF) and other professional organizations recommend that clinicians discuss chemoprevention with women at high risk.[6-8] An estimated 15% of women age 35 to 79 in the United States may be eligible for chemoprevention,[9] but less than 5% of women at high risk who are offered an antiestrogen for primary prevention agree to take it.[10] Compounding this underutilization is the large proportion of women who may be unaware of their high-risk status because of an inability to routinely screen for high risk in the primary care setting. Other reasons for low chemoprevention uptake include insufficient knowledge about antiestrogens on the part of clinicians and patients, multiple competing demands for PCPs, and concerns about side effects.[10,11] Even the term "chemoprevention" has negative connotations, because it sounds like "chemotherapy." The perception among patients and PCPs is that medications used to treat cancer and prescribed by oncologists may have

many toxicities. The risks and benefits of chemoprevention need to be placed in the context of pharmacologic interventions used to treat or prevent other chronic conditions (e.g., aspirin or statins for cardiovascular disease, bisphosphonates for osteoporosis). Further research is needed to determine how knowledge about breast cancer risk and chemoprevention options are best communicated to women to promote breast cancer prevention strategies.

BREAST CANCER RISK ASSESSMENT

Based on age and breast cancer risk, an estimated 15% of women in the United States meet high-risk criteria and may be eligible for chemoprevention.[9] Known breast cancer risk factors include family history, reproductive history, and lifestyle factors, such as alcohol intake and obesity.[12] Women with benign breast disease, such as atypical hyperplasia (AH) and lobular carcinoma in situ (LCIS), have up to a 4- to 10-fold increased risk of breast cancer.[13] Genetic determinants, such as germ-line mutations in the *BRCA1* and *BRCA2* genes, confer the greatest effect on breast cancer risk. The Gail model, or Breast Cancer Risk Assessment Tool, which takes

into account a woman's age, race, reproductive history, first-degree family history of breast cancer, and benign breast disease including atypia, is the most commonly used model in the United States and has been well validated at the population level.[14] It can be administered to women age 35 or older and provides an individual's absolute 5-year and lifetime risk of invasive breast cancer compared to women of the same age and race in the general population. High-risk criteria used to determine eligibility in chemoprevention trials are at least a 1.67% 5-year risk or 20% or greater lifetime risk of invasive breast cancer. To account for differences in breast cancer risk by race and ethnicity, the Gail model incorporated data from the Women's Contraceptive and Reproductive Experiences[15] and Asian American Breast Cancer Study[16] to provide more sensitive estimates for African American and Asian women, respectively. Few studies have used this model in Hispanic populations.[17,18] Hispanic women have significantly lower breast cancer risk compared to non-Hispanic white women; however, risk differs among Hispanic subgroups in the United States: according to the Gail model, Cubans have a higher 5-year risk (p < 0.05) and Dominicans have a higher lifetime risk than Mexicans (p < 0.001).[19] Interestingly, eligibility for chemoprevention among U.S. women varies dramatically by race and ethnicity, with 18.7% of whites, 5.7% of blacks, and 2.9% of Hispanics meeting high-risk criteria according to the Gail model.[9]

In women with a strong family history of breast cancer (i.e., two or more affected family members, particularly those with early-age onset), the Tyrer-Cuzick model is useful because it also accounts for second- and third-degree family history of breast and ovarian cancer and age at diagnosis.[20] This model may be particularly relevant for estimating risk in women with multiple affected family members, as well as LCIS. Women who had a 10-year risk of breast cancer of 5% of more according to the Tyrer-Cuzick model were included in the International Breast Cancer Intervention Study-I (IBIS-I) of tamoxifen and IBIS-II trial of anastrozole compared with placebo.[2,5] A comparison of the breast cancer risk factors included in the Gail and Tyrer-Cuzick models are summarized in Table 1.

High-risk benign breast disease is an important and under-recognized breast cancer risk factor.[21] Over one million benign breast biopsies are performed in the United States each year,[22] with approximately 10% showing AH or LCIS—conferring a relative risk of breast cancer of up to 4 to 10.[23-27] Long-term studies indicate that absolute breast cancer risk in women with AH is approximately 30% at 25 years of follow-up.[25,28] Of note, the Gail model significantly under-predicts breast cancer risk in women with AH (p < 0.001),[29] whereas the Tyrer-Cuzick model tends to over-predict risk.[30] Because of the high estrogen receptor (ER) expression in AH and the fact that the majority of breast cancers that develop in women with AH are ER+,[31] these high-risk women derive a greater benefit from chemoprevention than the general high-risk population. In the randomized, placebo-controlled chemoprevention trials, relative risk reduction of breast cancer among the subgroup of 2,009 women with AH ranged from 41% to 79%.[1,2,4,5,21] In a cohort study of women with atypical breast lesions, 10-year breast cancer risk with chemoprevention was 7.5%, compared to 21.3% without chemopreven-

KEY POINTS

- Breast cancer chemoprevention with antiestrogens is underutilized despite several randomized controlled trials demonstrating up to a 50% to 65% relative risk reduction of breast cancer incidence among women at high risk.
- Approximately 10 million women in the United States may be eligible for breast cancer chemoprevention, but less than 5% of women at high risk who are offered an antiestrogen for primary prevention agree to take it.
- Reasons for low chemoprevention uptake include lack of routine breast cancer risk assessment in the primary care setting, insufficient knowledge about antiestrogens on the part of clinicians and patients, and concerns about side effects.
- Interventions designed to increase identification of women at high risk and chemoprevention uptake, including written materials, decision aids, and incorporating breast cancer risk assessment tools into clinical practice, have met with limited success.
- Because of the proven efficacy of breast cancer chemopreventive agents, widespread use of antiestrogens for primary prevention among women at high risk has the potential to significantly improve the public health burden of this disease.

TABLE 1. Comparison of Breast Cancer Risk Factors in the Gail and Tyrer-Cuzick Models

Gail Model	Tyrer-Cuzick Model
Age (35 or older)	Age
Race/ethnicity (white, black, Hispanic, Asian American [Chinese, Japanese, Filipino, Hawaiian, other], unknown)	Ashkenazi Jewish descent
Age at menarche	Age at menarche
Age at first live birth	Age at first live birth
	Menopausal status
	Age at menopause
	Use of hormone replacement therapy
	Body mass index
Number of benign breast biopsies	
Benign breast biopsy with atypical hyperplasia (excludes LCIS, DCIS, or invasive breast cancer)	Benign breast biopsy including hyperplasia with or without atypia and LCIS
Number of first-degree relatives with breast cancer	Number of first-, second-, and third-degree relatives with breast or ovarian cancer, bilateral breast cancer, and age at diagnosis
	BRCA mutation status

Abbreviations: DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ.

tion.[24] Despite this evidence, chemoprevention uptake remains low among these women at high risk.[32]

BREAST CANCER CHEMOPREVENTIVE AGENTS
Selective Estrogen Receptor Modulators

Table 2 summarizes results of the major randomized controlled trials of SERMs and AIs for the primary prevention of breast cancer. In 1998, the Breast Cancer Prevention Trial (BCPT) demonstrated that the SERM tamoxifen taken for 5 years reduced breast cancer incidence in women at high risk by 49% (number needed to treat [NNT] to prevent one invasive breast cancer was 95 at 5 years and 56 at 10 years).[33,1] The overall results from three additional randomized controlled trials confirmed that tamoxifen decreased breast cancer risk by 30% to 40% compared to placebo.[34-37] In particular, long-term follow-up data (median of 16 years) from the IBIS-I trial demonstrated a persistent protective effect of tamoxifen (NNT was 22 at 20 years).[2] The magnitude of this risk reduction is comparable to what has been observed with preventive agents for cardiovascular disease.[38-40]

Another SERM, raloxifene, has been shown to reduce the incidence of breast cancer in postmenopausal women for the treatment and prevention of osteoporosis.[41,42] Updated analyses from the Study of Tamoxifen and Raloxifene (STAR) trial demonstrated that raloxifene had 76% of the efficacy of tamoxifen for breast cancer prevention among postmenopausal women at high risk with a more favorable side effect profile.[3] Based on the results of these trials, tamoxifen was approved by the U.S. Food and Drug Administration (FDA) for breast cancer risk reduction among women at high risk in 1998 and raloxifene in 2007.

Aromatase Inhibitors

Data from adjuvant trials have proven to be a useful model for assessing the chemopreventive effects of endocrine therapies, since results of antiestrogens in the primary prevention setting closely mirrored those for adjuvant treatment.[37] In 2011, results from the Mammary Prevention Trial-3 (MAP.3) demonstrated that the AI exemestane given to postmenopausal women at high risk reduced invasive breast cancer incidence by 65% compared to placebo (NNT was 26 at 5 years).[4] High-risk criteria included age 60 or older (49%), a 5-year Gail risk score 1.66% or greater (40%), AH or LCIS (8%), and ductal carcinoma in situ treated with mastectomy (3%).[4] After a median follow-up of 35 months, 11 invasive breast cancers occurred in the exemestane arm compared to 32 in the placebo group (annual incidence of 0.19% vs. 0.55%; p = 0.002).[4] In the group comparing exemestane compared to placebo, more grade 2 or higher arthritis (6.5% vs. 4.0%) and hot flashes (18.3% vs. 11.9%) were seen. However, overall quality of life did not differ between the two arms, and no significant differences in new-onset osteoporosis, clinical skeletal fractures, cardiovascular events, or other malignancies were seen.

Another third-generation AI was investigated in the IBIS-II trial, which randomly assigned postmenopausal women at high risk, age 40–70, to receive either anastrozole or placebo for 5 years.[5] With a median follow-up of 5 years, 40 breast cancers (invasive and noninvasive) occurred in the

TABLE 2. Updated Results from Major Randomized Controlled Trials of Selective Estrogen Receptor Modulators and Aromatase Inhibitors for Breast Cancer Chemoprevention

Trial	No. of Participants	Eligibility, High-Risk Criteria for Breast Cancer	Intervention	Median Follow-up (Months)	Breast Cancer Incidence	Breast Cancer Risk Reduction RR or HR (95% CI)
BCPT, 2005[1]	13,388	Age ≥ 35, 5-yr Gail risk score > 1.66% if age 35-59 or ≥ 60 or LCIS	Tamoxifen 20 mg/d x 5 yrs versus placebo	84	3.59 versus 6.29[a]	0.57 (0.46-0.70)
IBIS-I, 2014[2]	7,154	Age 35-70, 10-fold risk if age 35-39, or 4-fold risk if age 40-44, or 2-fold risk if age 45-70	Tamoxifen 20 mg/d x 5 yrs versus placebo	192	7.0% versus 9.8%[b]	0.71 (0.60-0.83)
STAR, 2010[3]	19,747	Age ≥ 35, postmenopausal, 5-yr Gail risk score > 1.66%	Raloxifene 60 mg/d versus tamoxifen 20 mg/d x 5 yrs	81	5.02 versus 4.04[a]	1.24 (1.05-1.47)
MAP.3, 2011[4]	4,560	Age ≥ 35, postmenopausal, 5-yr Gail risk score > 1.66% if age 35-59 or age ≥ 60 or AH, LCIS, DCIS with mastectomy	Exemestane 25 mg/d x 5 yrs versus placebo	35	0.19% versus 0.55%[c]	0.35 (0.18-0.70)
IBIS-II, 2013[5]	3,864	Age 40-70, postmenopausal, 4-fold risk if age 40-44, or 2-fold risk if age 45-59, or 1.5-fold risk if age 60-70	Anastrozole 1 mg/d x 5 yrs versus placebo	60	2% versus 4%[b]	0.47 (0.32-0.68)

Abbreviations: SERM, selective receptor estrogen modulators; AI, aromatase inhibitor; AH, atypical hyperplasia; BCPT, Breast Cancer Prevention Trial; CI, confidence interval; DCIS, ductal carcinoma-in-situ; HR, hazard ratio; IBIS, International Breast cancer Intervention Study; LCIS, lobular carcinoma in situ; MAP, Mammary Prevention Trial; RR, relative risk; STAR, Study of Tamoxifen and Raloxifene.
[a]Invasive breast cancer incidence rate/1,000 women.
[b]All breast cancers, invasive and noninvasive.
[c]Annual incidence of invasive breast cancers.

anastrozole arm compared to 85 in the placebo group (hazard ratio 0.47; 95% confidence interval 0.32–0.68; p < 0.0001). In the anastrozole group compared to placebo, more arthralgia (51% vs. 46%), vasomotor symptoms (57% vs. 49%), vaginal dryness (19% vs. 16%), and hypertension (5% vs. 3%) occurred. In general, there appear to be fewer serious side effects with AIs compared to tamoxifen.

To date, there are no head-to-head trials comparing SERMs to AIs or evaluating extended hormone therapy for up to 10 years in the primary prevention setting. Also, these antiestrogens have no effect on the incidence of ER– tumors, which are associated with a poorer prognosis compared to ER+ breast cancer and are more common in younger women, black women, and *BRCA1* mutation carriers. In addition, limited data exist on the efficacy of antiestrogens for breast cancer risk reduction in women with hereditary breast cancer syndromes, such as *BRCA1* and *BRCA2* mutation carriers.[43,44] Of note, none of these chemoprevention trials were adequately powered to detect a difference in breast cancer–specific or overall mortality.

Chemoprevention Guidelines

Based on this evidence, the USPSTF, American Society of Clinical Oncology, and the National Comprehensive Cancer Network published consensus guidelines on breast cancer chemoprevention.[6-8] Premenopausal and postmenopausal women at high risk, defined as a 5-year Gail risk 1.67% or greater or LCIS, may take tamoxifen for 5 years for the primary prevention of breast cancer. Younger women (age 35–50), those without a uterus, and those at higher risk for breast cancer derive the greatest clinical benefit from tamoxifen. Postmenopausal women at high risk also have the options of raloxifene, exemestane, and anastrozole for breast cancer risk reduction. Because of the increased risk of uterine cancer, follow-up for women on tamoxifen should include annual gynecologic examinations with a timely work-up of abnormal vaginal bleeding, but routine endometrial biopsies in the absence of vaginal symptoms is not recommended. SERMs are contraindicated in women with a history of thromboembolism, such as deep vein thrombosis, pulmonary embolus, stoke, or transient ischemic attack. In addition, the STAR trial excluded women with uncontrolled diabetes or hypertension, those with atrial fibrillation, and those on hormone replacement therapy.[45]

Figure 1 depicts a potential algorithm for clinical decision making about antiestrogens for breast cancer chemoprevention based on menopausal status, history of thromboembolism, risk of osteoporosis, and prior hysterectomy. For premenopausal women at high risk, tamoxifen is currently the only FDA-approved drug for the primary prevention of breast cancer. Younger women (age 35–50) at high risk derive the greatest clinical benefit from tamoxifen because the risk of serious side effects, such as thromboembolism and uterine cancer, is negligible compared to placebo. For postmenopausal women at high risk with an intact uterus, raloxifene may be favored over tamoxifen, whereas tamoxifen may be preferable in women with a prior hysterectomy because of

FIGURE 1. Choice of Selective Estrogen Receptor Modulator or Aromatase Inhibitor for Breast Cancer Chemoprevention
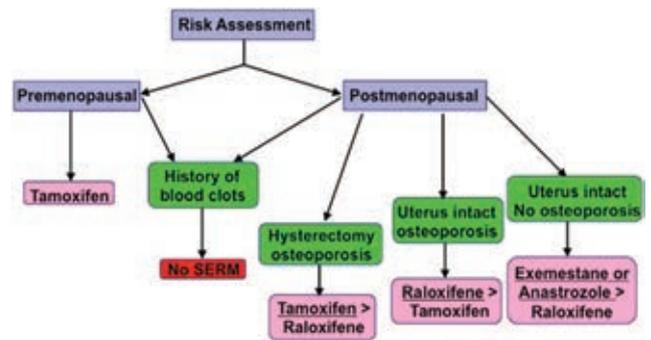
Choice is based on menopausal status, history of thromboembolism, prior hysterectomy, and risk of osteoporosis (based upon the author's personal algorithm and not a guideline recommendation).

its greater efficacy in breast cancer risk reduction.[3] Both SERMs are contraindicated in women with a prior history of thromboembolism, but AIs may be offered to postmenopausal women. SERMs may be favored over AIs among postmenopausal women at high risk with low bone density, although presence of osteoporosis is not an absolute contraindication to taking an AI. Overall, both SERMs and AIs are effective chemopreventive agents; therefore, the choice will depend on personal preferences and acceptable toxicity profiles.

BARRIERS TO UPTAKE OF BREAST CANCER CHEMOPREVENTION

Low Uptake of Breast Cancer Chemoprevention

An estimated 10 million U.S. women age 35 to 79 are eligible for breast cancer chemoprevention.[9] Based on a systematic review and meta-analysis of patient decisions about chemoprevention, less than 5% of women at high risk who are offered an antiestrogen for primary prevention agree to take it.[10] The main reason for this is the perception of patients and physicians that chemoprevention does not offer a favorable risk–benefit profile.[46-49] After the 1999 FDA approval of tamoxifen for primary prevention in women at high risk, data from the National Health Interview Survey indicated that the prevalence of tamoxifen use among women without a personal history of breast cancer was 0.2% in 2000 and decreased to 0.08% in 2005.[32] Similarly, after raloxifene's FDA approval in 2007, its use for breast cancer risk reduction decreased.[45] It remains to be seen whether there will be greater acceptance of AIs for primary prevention.

Lack of Routine Breast Cancer Risk Assessment in Clinical Practice

Despite the online availability of both the Gail and Tyrer-Cuzick models, only 18% of PCPs report use of software to calculate breast cancer risk.[50] In a cross-sectional survey of over 300 PCPs, use of the Gail model for breast cancer risk

assessment varied by medical specialty (37% internal medicine, 33% family medicine, 60% gynecology), as well as ever recommending or prescribing breast cancer chemoprevention (9% internal medicine, 8% family medicine, 30% gynecology).[51] Barriers to routine breast cancer risk assessment in the primary care setting include time constraints during clinic visits and lack of familiarity with risk assessment tools and chemoprevention.[52] There may also be concerns about the accuracy of breast cancer risk prediction models.

Risks and Benefits of Chemoprevention

Concerns about potential side effects, such as uterine cancer, thromboembolic events, and menopausal symptoms, are the main contributors to a woman's unwillingness to initiate chemopreventive agents for breast cancer and a physician's reluctance to prescribe them.[46-48,53-56] In the BCPT, the net benefit achieved with tamoxifen varied by age, race, and level of breast cancer risk, such that an estimated 2.5 million women in the United States could derive a net benefit from the drug.[1] In the STAR trial, raloxifene was associated with a lower risk of thromboembolic events, benign uterine complaints, and cataracts than tamoxifen.[45,57] Although women on tamoxifen reported more gynecologic and vasomotor symptoms,[45] overall quality of life was similar for both SERMs.[57] In the MAP.3 and IBIS-II trials, AIs decreased bone mineral density compared to placebo but did not increase the risk of fractures.[4] In contrast, SERMs have a favorable effect on bone density with about a 32% reduction in fracture incidence.[33,41,42]

The general perception among patients and providers is that use of antiestrogens for primary prevention does not confer a favorable risk–benefit profile. Based on results from the STAR trial, per 1,000 women at high risk, tamoxifen would prevent 40 breast cancers compared with causing 2.25 uterine cancers and 3.3 thromboembolic events, whereas raloxifene would prevent 31 breast cancers compared with causing 2.47 thromboembolic events.[3] Freedman et al developed a model to predict the risks and benefits of SERMs for women older than 50 based on age, race/ethnicity, breast cancer risk, and presence of a uterus, which may provide a more personalized risk–benefit profile.[58] Whereas the side effects diminish after stopping chemoprevention, the protective effect on breast cancer risk persists after discontinuation.[36] Unlike preventive therapies for other chronic diseases, which often require life-long treatment, breast cancer chemoprevention for 5 years can confer long-term benefits with side effects limited to during active treatment.

Low chemoprevention uptake occurs because of the lack of effective strategies to inform both PCPs and women at high risk about the risks and benefits of antiestrogens. Physicians who felt insufficiently informed about risk-reducing options were less than half as likely to prescribe a SERM for breast cancer prevention than physicians who felt sufficiently trained.[59] Physician recommendation and health care provider communication are among the most influential factors to influence chemoprevention uptake.[46,48,60]

Lack of Intermediate Biomarkers to Predict Response to Chemopreventive Agents

The lack of well-validated intermediate biomarkers for short-term breast cancer risk assessment, analogous to low-density lipoprotein cholesterol for cardiovascular disease or T-score on a bone density scan for osteoporosis, is another barrier to uptake of antiestrogens. Even if a woman at high risk agrees to take chemoprevention, there is no way to assess whether she is deriving a benefit from the agent except with long-term follow-up to determine whether she remains free of breast cancer. Mammographic density (MD), a strong predictor of breast cancer risk,[61,62] may also serve as a predictive biomarker of response to breast cancer chemoprevention. In the IBIS-I trial, tamoxifen given for 18 months caused a significant decrease in MD compared to placebo, particularly among premenopausal women (p < 0.001).[63] Cuzick et al demonstrated that at least a 10% reduction in MD with tamoxifen was associated with a 63% reduction in breast cancer risk.[64] Compared to other qualitative methods of measuring MD, the Cumulus technique provides quantitative measurements and has been strongly associated with breast cancer risk in epidemiologic studies.[65,66] However, more automated methods for measuring MD or volumetric density are needed, which would be applicable in the clinical setting.[67,68]

Measurement of endogenous hormone levels, such as plasma estrone sulfate, testosterone, prolactin, and sex hormone-binding globulin, have been shown to improve breast cancer risk prediction in postmenopausal women.[69] Changes in estradiol and testosterone levels may also serve as good breast cancer risk biomarkers for weight loss interventions.[70] However, assay variability with low hormone levels, particularly in postmenopausal women, may hamper their clinical utility.[71]

Predictors of Poor Adherence to Endocrine Therapy

The effectiveness of chemoprevention depends not only on initiation of therapy but also on long-term adherence. In the chemoprevention trials, adherence at 5 years ranged from 64% to 85%[1,4,36,57]; however, clinical trial participants are often more compliant than the general population. Veronesi et al reported that women in a chemoprevention trial were less likely to adhere to tamoxifen than patients with breast cancer treated in the adjuvant setting.[72] In the Sister Study cohort, 46% of women taking tamoxifen for primary prevention discontinued within 4.5 years.[73] In BCPT and MAP.3, ethnic minorities and women with low income had less drug adherence.[74,75] Women from racial/ethnic minorities and those who are uninsured are less likely to seek breast cancer preventive care, perhaps contributing to higher rates of late-stage diagnosis.[76,77] Understanding predictors of poor uptake and adherence to breast cancer chemoprevention will aid in the development of targeted interventions for certain patient subgroups.

INTERVENTIONS TO INCREASE UPTAKE OF BREAST CANCER CHEMOPREVENTION

Results from recent intervention trials to increase chemoprevention uptake targeting both patients and providers are summarized in Table 3. In a recent randomized controlled trial of a web-based decision aid that informed women about the risks and benefits of SERMs,[78] only 0.5% of eligible participants had started raloxifene and none had started tamoxifen. In a study called the "Ready, Set, GO GAIL!" project, PCPs systematically screened more than 5,700 women age 35–70 with the Gail model; 868 (15.2%) met high-risk criteria and were eligible for chemoprevention, only 128 (14.7%) of these women were referred for specialized risk counseling, 60 (6.4%) completed the consultation, and 17 (2%) started a SERM.[79] In the BreastCARE intervention trial, women in the primary care setting were randomly assigned to usual care or a tablet-based patient intake tool that generated individualized breast cancer risk profiles for patients and their physicians.[80] Although more women at high risk were referred for specialized risk counseling with the intervention compared to the control arm (18.8% vs. 4.1%), discussions about chemoprevention were still limited (1% vs. 0%).

Interventions designed to increase chemoprevention uptake, involving reading materials or decision aids, met with limited success, ranging from 0.5% to 5.6%.[48,49,55,78,81] Few studies have assessed the effect of automated decision support for PCPs.[82,83] Two studies used a computer-based tool to improve referrals for genetic testing, but they were not integrated into clinic workflow.[84] Given that breast cancer chemoprevention is not widely diffused in the primary care setting, more effective tools are needed to accurately identify women at high risk and educate both patients and providers about the risks and benefits of chemoprevention options. Studies that involved consultation at a breast clinic reported chemoprevention uptake ranging from 11% to 58%.[46,53,54,60,85-87] Therefore, higher chemoprevention uptake may be achieved with health professionals who have sufficient knowledge and training about breast cancer risk and risk reduction strategies. Given that many community practices may not have access to high-risk clinics, PCPs need to be at the front line of chronic disease prevention, including breast cancer chemoprevention.

Strategies to minimize toxicities to antiestrogens include administering lower or intermittent dosing, developing alternative drug delivery methods such as topical therapy, and identifying novel chemopreventive agents with fewer side effects. For example, clinical trials of oral low-dose tamoxifen of 1, 5, or 10 mg daily or 10–20 mg weekly have demonstrated similar biologic efficacy to standard-dose tamoxifen (20 mg daily) with fewer side effects.[88-95] Since tamoxifen is a prodrug that requires hepatic activation, Mauvais-Jarvis et al developed a topical form of trans-4-hydroxytamoxifen (4-OHT), the active metabolite of tamoxifen, which would maximize local drug levels with fewer systemic side effects.[96] Thus far, topical tamoxifen has been tested for the treatment of mastalgia[97] and in two presurgical (window of opportunity) trials in women with breast cancer.[98,99] Finally, novel chemopreventive agents—including aspirin, NSAIDs, metformin, vitamin D, and vaccines to tumor-associated antigens—which may have a more favorable side effect profile compared to SERMs and AIs and perhaps activity against ER– breast cancers, are currently under investigation.[100]

CONCLUSION

Breast cancer chemoprevention with antiestrogens has proven efficacy in high-risk populations, but uptake remains low. Preventive therapy for cancer is currently less well established compared to other chronic conditions, such as cardiovascular disease, and could benefit from lessons learned.[101] Health care providers can do more in the area of cancer prevention by identifying high-risk populations in the primary care setting. Chemoprevention needs to be integrated into broader strategies of preventive care, which may include nonpharmacologic interventions such as lifestyle modification. Given the high compliance rates for breast cancer screening, incorporating formal risk assessments at the time of screening mammography may represent a "teachable moment" when women are already engaging in a health behavior related to breast cancer. Novel health information technologies such as electronic health records and patient health portals may be a method for integrating information about breast cancer risk and chemoprevention into clinic workflow.

TABLE 3. Intervention Trials to Increase Uptake of Breast Cancer Chemoprevention

Authors, Year	No. of Participants	Eligibility	Intervention	Outcomes
Fagerlin et al 2011[79]	1,197	Age 40-74, postmenopausal, 5-yr Gail risk score > 1.66%	Tailored online decision aid "Guide to Decide"	0% tamoxifen and 0.5% (2 patients) raloxifene uptake with intervention
Owens et al 2011[80]	868	Age 35-70, 5-yr Gail risk score ≥ 1.7% or lifetime risk ≥ 20%	"Ready, Set, GO GAIL!" project, clinic-based intervention to implement Gail model in women's health clinic	Completion of high-risk consultation, 6.4% (60 patients); chemoprevention uptake, 2% (17 patients)
Kaplan et al 2014[81]	1,235	Age 40-74, scheduled for clinic visit at two primary care practices, spoke English, Spanish, or Chinese	BreastCARE, tablet-based breast cancer risk assessment that generated individualized reports for patients and their physicians	Referral to high-risk clinic, 18.8% versus 4.1% among women at high risk (307 patients); discussion of chemoprevention, 1% versus 0%

Breast cancer incidence continues to increase in most countries,[102] and the economic burden of cancer in the United States is expected to substantially increase[103] because of greater intensity of health care usage[104,105] and increasing costs of cancer care.[106-109] These rising medical costs will disproportionately affect racial/ethnic minorities and low-income and under-insured individuals. U.S. health care providers can do more in the area of cancer prevention by targeting high-risk populations. Promoting chemoprevention uptake among women at high risk will require a major paradigm shift in clinical practice if antiestrogens are to be widely adopted in the primary care setting.

Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

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Decision Making in the Context of Breast Cancer Chemoprevention: Patient Perceptions and the Meaning of Risk

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OVERVIEW

Chemoprevention with selective estrogen receptor modulators (SERMs) is considered one of the most promising risk reduction options to date in the United States. Tamoxifen and raloxifene are both approved by the U.S. Food and Drug Administration (FDA) for breast cancer risk reduction. However, despite endorsement from the American Society for Clinical Oncology and the National Comprehensive Cancer Network, uptake remains low. Decision aids have been successful in improving women's understanding and knowledge about the risk–benefit trade-offs in decision making regarding SERMs. However, increased knowledge does not lead to increased uptake of chemoprevention for the purpose of reducing breast cancer risk; instead, women become more reluctant to take medication that is itself associated with risks. Reasons for this include a lack of awareness that SERMs are effective in reducing breast cancer risk, an unwillingness to increase the risk of other disease, reluctance to take a daily medication, and the perception of tamoxifen as a "cancer drug." In studies on hypothetical decision making in the context of chemoprevention women indicate greater willingness to take a SERM when they are determined to be at risk. These findings suggest a differential understanding of what risk means among the general public, health professionals, and researchers. *Feeling* at risk is related to bodily signs and symptoms and not to population-derived probabilities. Such differential understanding may in part explain women's perception of the low efficacy of SERMs and their decision making regarding SERM use.

Breast cancer is the leading cancer in females and is responsible for the greatest number of cancer deaths among women worldwide,[1] including the United States.[2] According to data for 2008 to 2010 collected in the Surveillance, Epidemiology, and End Results (SEER) program, 12.3% of women in the United States will be diagnosed with breast cancer during their lifetime. There is conflicting evidence as to whether changing behavioral factors such as a sedentary lifestyle, smoking, or regular alcohol consumption can reduce the risk of breast cancer.[3-6] Risk reduction efforts for breast cancer therefore pose a challenge, especially as the most effective options (young age at first live birth and having multiple children) conflict with other public health messages and efforts.[7] In this context, chemoprevention with selective estrogen receptor modulators (SERMs) is considered one of the most promising risk reduction options to date in the United States. At the present time two SERMs—tamoxifen and raloxifene—are approved by the U.S. FDA for breast cancer risk reduction, although other medications are under investigation.[8] Leading oncologic organizations such as the American Society for Clinical Oncology and the National Comprehensive Cancer Network recommend the use of these medications for prevention of breast cancer. Uptake, however, has lagged behind expectations.[9]

Tamoxifen was the first medication to be approved for breast cancer risk reduction. The Breast Cancer Prevention Trial (BCPT) conducted between 1992 and 1998 in the United States showed that among women with an increased risk of developing breast cancer, those who had taken tamoxifen saw a risk reduction of 50% compared to those in the control group.[10] The risk reduction among women with a diagnosed atypia such as lobular carcinoma in situ (LCIS) or atypical hyperplasia (AH) was even greater: 56% and 86% respectively. Since these findings, a range of other drugs to reduce breast cancer risk have been under investigation.[8] Thus far, only raloxifene has been approved, after the Study of Tamoxifen and Raloxifene (STAR) conducted in the early 2000s in the United States established the efficacy of raloxifene in reducing breast cancer risk.[11] Risk reduction among women with LCIS or AH was lower in the STAR than in the BCPT, although these women still showed a higher level of risk reduction than women whose increased risk assessment was based on the Gail score alone. As follow-up of both of these studies continues, the risks and benefits associated with both drugs and their effects on breast cancer risk reduction are expected to change over time.[12]

PREVALENCE OF SERM USE FOR BREAST CANCER RISK REDUCTION

In a series of studies conducted using data from the National Health Interview Study, Waters et al[13,14] estimated the prev-

alence of tamoxifen and raloxifene use in the United States. In 2010, only 0.03% of women age 35 to 79 reported taking tamoxifen and 0.21% of women age 50 to 79 reported taking raloxifene for the prevention of a primary invasive breast tumor.[14] This compares to the approximately 15% of all U.S. women age 35 to 79 who would have been eligible to take tamoxifen in 2000 and the 5% who would have had a positive risk/benefit index.[15]

The abovementioned studies provide the only available population-based data on the use of SERM drugs for breast cancer risk reduction. However, several studies have investigated the uptake of SERMs by individuals in high-risk clinics and primary care. Uptake in these studies is variable.[16] For example, Tchou et al. studied the medical records of women who sought risk evaluation at a breast clinic in a metropolitan area of the United States and found that 42% of women who were offered tamoxifen by their physicians actually took the drug.[17] Older age and a history of LCIS or AH were predictive of tamoxifen acceptance. In a separate study conducted by Kay et al.,[18] women who had been evaluated in a breast clinic in Canada and who showed either an increased risk of developing breast cancer or had a diagnosis of AH were approached and given a decision guide on the risks and benefits of tamoxifen. In this sample, among which 60% of women had a diagnosis of AH, only 6 out of 51 eligible women (11.8%) chose to take tamoxifen.[18,19] Finally, uptake was 10.6% in a more recent study in a high-risk breast clinic in the United Kingdom. Eligibility criteria for women to participate in the study were based on an increased risk as calculated by the Tirer-Cuzick model, and all women had previously been monitored for their breast cancer risk.[20] Those who decided to take tamoxifen were older and showed a trend toward higher risk scores compared to those who chose not to take the drug.

DECISION MAKING ON SERM USE

Decision making in the context of breast cancer risk and SERM use includes the evaluation of complex risk–benefit trade-offs.[21,22] Both of the approved medications, tamoxifen

and raloxifene, carry significant risks, including endometrial cancer (particularly for tamoxifen), thromboembolic events, stroke, and cataracts.[8,12,21]

Several decision aids have been developed that aim to provide neutral information and present the involved risk–benefit trade-offs in SERM decision making. Few of them, however, include personalized risk and benefit information; exceptions are the decision aids developed by Fagerlin et al[23,24] and Ozeanne et al.[25,26]

The two decision aids developed by Fagerlin et al are particularly aimed at helping women decide whether to take tamoxifen and/or raloxifene as a treatment option to reduce breast cancer risk. They both consist of personalized information on breast cancer risk; in addition, one also includes information on the risks and benefits associated with taking tamoxifen whereas the second provides comparative information on the risk–benefit profiles of tamoxifen and raloxifene.[23,24] For the decision aid looking at tamoxifen alone, overall the women who participated in testing the decision aid were not interested in taking the drug. Among those who were interested (5.8% indicated that they were likely to take the drug in the next year), fewer women had high knowledge scores than in the overall sample. Thus, increased knowledge of tamoxifen and its associated risks seemed to decrease women's willingness to take the chemoprevention agent. The same was true for the decision aid that offered information on both tamoxifen and raloxifene.[23] The authors investigated the reasons why women may not be interested in taking the drugs and found that the majority did not perceive them as likely to reduce their breast cancer risk. Furthermore, the study sample had a majority of women with a risk score for developing breast cancer within the next 5 years of 3% or lower according to the Gail model. The authors hypothesized that for the women in the study, this risk was considered so low that it simply did not warrant taking medicines, especially ones that have potentially significant side effects.[23] It has also been suggested that lack of knowledge about the option of chemoprevention is one reason for the low uptake. Although this may be the case, it is important to consider that increased knowledge about tamoxifen and/or raloxifene may in fact lead to a decrease in willingness to take either drug.[22]

The main goal of the decision aid developed by Ozeanne et al is to provide breast cancer risk information in context, and this aid therefore includes a range of treatment options such as chemoprevention and mastectomy, as well as other disease risks.[25,26] Although the feasibility and usability of the tool have been tested, full evaluations have not yet been published. Deciding on treatment options for breast cancer risk reduction is considered a preference-sensitive decision because of the complex risk–benefit trade-offs that are involved.[27] This means that the decision is, and should be, based on an individual's preferences rather than on population-based standards. Such a decision nevertheless also presupposes an individual's understanding of the risks and benefits involved. The existing decision aids do seem to be able to educate women adequately about the risks and

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KEY POINTS

- Decision making in the context of breast cancer chemoprevention includes complex risk–benefit trade-offs.
- The decision should be based on individual preferences.
- Increased knowledge on chemoprevention may deter women from taking drugs for breast cancer prevention.
- Perceptions of low efficacy, worries about side effects, and the notion of tamoxifen as a cancer drug have all been suggested as factors influencing women's decision making regarding chemoprevention for breast cancer risk reduction.
- Understandings of risk differ between health care providers and laywomen.

benefits.[22] However, to truly understand, evaluate, and predict the uptake of SERM drugs, it may be crucial to understand women's perceptions of chemoprevention, as these are likely to influence decision making.

PERCEPTIONS OF CHEMOPREVENTION

Below are presented some of the prevailing perceptions, assumptions, and beliefs about chemoprevention, as revealed by research to date. However, most of this research has looked only at tamoxifen. The study of Fagerlin et al[23] provides one of the few exceptions, from which we may also learn about perceptions of raloxifene.

What's in a Name? Tamoxifen and Chemoprevention

Tamoxifen has been used for several decades in the treatment of breast cancer to prevent the recurrence of disease. For some women, tamoxifen is therefore associated with cancer and is considered a "cancer drug."[20] These women expressed the fear that if they took tamoxifen, others may conclude that they have breast cancer. Because of the perception of tamoxifen as a cancer drug and confusion over the difference between chemotherapy and chemoprevention, some women have expressed fear of hair loss or other side effects that are more often associated with chemotherapy.[20,28]

Side Effects

Several studies have shown that women are concerned about the side effects of SERM use.[18,29] Moreover, these concerns are not only related to the severe side effects such as endometrial cancers, but also to the more common but less serious effects of taking the drugs, such as hot flashes. For example, one nested qualitative study reported that participants in focus group discussions were reluctant to end hormone replacement therapy in favor of chemoprevention.[29] SERMs may induce hot flashes, which are reduced by hormone replacement therapy. Although hot flashes may not be considered serious from a medical point of view, they can impair a woman's day-to-day activities and reduce quality of life.

Risk Perception

Many women's perception of their breast cancer risk differs from the objective risk estimates derived from personalized risk assessments such as the Gail score or Claus model. Indeed, when objective breast cancer risk estimates are compared to women's own estimates, women regularly overestimate their personal risk level.[30] This generally high level of risk perception may influence a woman's decision making about chemoprevention. When women receive their objective personalized risk estimate they may be surprised by the relatively low values, and this may deter them from taking preventive action that could increase the risk of other diseases.[23,24,31-33]

On the other hand, there is evidence that women may not necessarily believe the risk levels provided through personalized risk estimates.[34] Furthermore, women's personal assessments of their risk have been shown to be extremely persistent and may not change through counseling. In one study, for example, among women attending a high-risk clinic in the United States to discuss their breast cancer risk and treatment options the women's preferences regarding chemoprevention were shown to be stable over time. The women were surveyed before and after the consultation, and their level of breast cancer risk that would indicate chemoprevention uptake was similar at both points.[27] In this study, 75% of the women indicated that they would take chemoprevention for breast cancer risk reduction if their lifetime risk of developing breast cancer was estimated at 60%. In comparison, the actual average risk in this sample of high-risk women was 18.5% (as determined by the Gail score).

Efficacy

It has been suggested that women might not believe that taking a chemopreventive agent will substantially reduce their breast cancer risk.[18,23] Such assumptions may be related to the low absolute risk scores of most of the women whose decision making patterns regarding chemoprevention have been studied. An accurate understanding of one's risk of developing breast cancer may therefore lead to the belief that the risk is too small to warrant action, particularly if such action in itself involves risks.

Taking Medicines

The idea of taking medication on a daily basis over a period of 5 years may be seen by some women as a constant reminder of their breast cancer risk and the potential of developing the disease.[20] This has been shown to be considered a drawback by some women when considering chemoprevention. Other studies have found that women are reluctant to take medicine in general because it is seen as "unnatural."[28] A general aversion to taking medicines has also been described in other contexts. This reluctance might be heightened for medicines that are not perceived as "necessary." Such generalized attitudes toward medications are likely to influence the perception of chemoprevention drugs and thus affect the overall acceptance of their use. This example also highlights the importance of viewing something (such as a medicine) as necessary in order to consider taking it.

WHAT CONSTITUTES A RISK?

Findings of the numerous studies and papers that have been published on women's decision making approaches to chemoprevention for breast cancer can be summarized as follows: increased knowledge and understanding of the risks and benefits involved in taking SERMs does not lead to increased uptake of chemoprevention for the purpose of reducing breast cancer risk[16]; instead, women become more reluctant to take medication with risks involved.[23,24,35]

At the same time, studies that have looked at the *intention* to take chemoprevention have regularly found higher num-

bers of women interested in and willing to take chemoprevention drugs compared to studies that have assessed *actual* behavior.[16,31,35,36] Kaplan et al[35] and Salant et al[37] present studies that may be illuminating in this regard. To study potential acceptance of chemoprevention in a sample of women with diverse ethnic and racial backgrounds, Kaplan et al surveyed women through their primary care networks. The authors developed a generic information guide on tamoxifen that included information on who is at high risk for breast cancer, the ability of tamoxifen to reduce breast cancer risk, and the drug's side effects. These facts were all presented as probabilities using an easy to understand visual format. In this study, more than 40% of women indicated that they would be likely or very likely to take tamoxifen if they were determined to be at high risk of breast cancer. When reading these study results, however, one must take into account the fact that the women sampled were not high risk, but women in the general population, and thus they merely *hypothesized* that *if* they were at high risk, they would be likely to take the drug. Given this fact, and in the light of some of the previously presented studies, one may ask what "to be at risk of developing breast cancer" actually means to laywomen, health professionals, and researchers.

The study of Salant et al[37] found that risk meant different things to the medical staff and to the women deemed to be at risk by the medical staff. Although the women were aware of their objective risk estimate level, they were more concerned about their personal feelings regarding being at risk, which were influenced by bodily signs and symptoms and not by population-derived probabilities. *Feeling* at risk is thus likely to be very different from being *told* that one is at risk.[38]

The term "risk" means very different things in epidemiology and medical care compared to everyday language. In everyday language, risk is typically associated with danger.[39] A probability of 1.66% may therefore not feel like much of a risk at all. When women answer that they would take action if determined to be at risk, it is thus very likely that they have other constructs in mind than the probabilistic concepts of the Gail model. For example, Dillard et al[40] found an association between anxiety and women's intention to gather additional information about tamoxifen and take the drug in the next few months. The psychological construct of anxiety may be more similar to individuals' connotations of risk than probabilistic concepts of risk and risk perception.

DECISION MAKING

As discussed above, decision making about whether or not to take chemoprevention to reduce breast cancer risk involves complex risks and trade-offs and should be based on an individual's preferences rather than on population-based standards. The prerequisite to enable such decision making is presentation of the involved risks and benefits in a way that is understandable, even to low-numerate populations.[41] Nevertheless, even when risks and benefits appear to be understood, willingness to take chemoprevention remains low among women who are eligible on the basis of their Gail score. Other research has shown that health decision making may not be based on an accurate understanding of risk information, but perhaps more on heuristics and feelings.[42,43] Feelings, assumptions, and experiences influence how risk information is perceived. As such, individuals may not always use the risk information presented to them in the ways that health care providers intend.[44]

The accumulating evidence that personalized risk information may not be as successful as previously thought in initiating particular health behaviors may also point to an increasing gap between approaches to treatment decision making using personalized risk information as advocated in health care, and the approaches of the individuals, which rely on feelings and heuristics. Various perceptions surrounding chemoprevention—that tamoxifen is a "cancer drug," fear of medication side effects, differences in the understanding of risk between laywomen and health care providers, a lack of knowledge about chemoprevention, and societal opinions of medication intake—provide the framework within which decision making takes place. Health care providers should be aware that counseling may be neither as effective nor as influential in terms of decision making as they assume,[27] since decisions may be based on perceptions that are influenced by an individual's family history, societal assumptions, and culture as much as, or even more than, the information and guidance offered by individual health care providers.[45]

IMPLICATIONS

There are several avenues through which women may be diagnosed as being at an increased risk for developing breast cancer and offered SERM treatment for risk reduction. For example, a family history of the disease, positive genetic evaluation, a history of LCIS or AH, or a Gail score higher than 1.66% are all indications for offering women SERMs as a treatment option. The risk–benefit trade-offs vary depending on the avenue through which a woman comes to be at risk for breast cancer. These different reasons for being or becoming at risk may also be important for decision making in this context since they may influence how an individual perceives the risk and, perhaps more importantly, to what degree she *feels* at risk.

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CANCER PREVENTION, GENETICS,
AND EPIDEMIOLOGY

Early Detection of Cancer: Past, Present, and Future

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OVERVIEW

Screening in both healthy and high-risk populations offers the opportunity to detect cancer early and with an increased opportunity for treatment and curative intent. Currently, a defined role for screening exists in some cancer types, but each screening test has limitations, and improved screening methods are urgently needed. Unfortunately, many cancers still lack effective screening recommendations, or in some cases, the benefits from screening are marginal when weighed against the potential for harm. Here we review the current status of cancer screening: we examine the role of traditional tumor biomarkers, describe recommended imaging for early tumor surveillance, and explore the potential of promising novel cancer markers such as circulating tumor cells (CTC) and circulating tumor DNA. Consistent challenges for all of these screening tests include limited sensitivity and specificity. The risk for overdiagnosis remains a particular concern in screening, whereby lesions of no clinical consequence may be detected and thus create difficult management decisions for the clinician and patient. If treatment is pursued following overdiagnosis, patients may be exposed to morbidity from a treatment that may not provide any true benefit. The cost-effectiveness of screening tests also needs to be an ongoing focus. The improvement of genomic and surveillance technologies, which leads to more precise imaging and the ability to characterize blood-based tumor markers of greater specificity, offers opportunities for major progress in cancer screening.

Perhaps no topic in oncology generates as much energy, angst, and debate as cancer screening and surveillance. Nearly all patients, clinicians, and researchers hope for medical tests that might diagnose cancer earlier or detect recurrence sooner, improve prognosis, and thus allow for increased cure rates. The effect of cancer on society is enormous— over 1.6 million individuals are diagnosed with cancer every year in the United States,[1] and one-half of men and one-third of women have a lifetime cancer risk. Screening in both healthy and high-risk populations offers the opportunity to detect cancer early, at a stage before symptom onset, and ideally before metastasis. Early detection of cancer may lead to decreased morbidity with improved survival, and in some situations treatment may require only surgery if identified early enough. This review covers three aspects of screening and early tumor surveillance including tumor biomarkers, imaging, and circulating tumor cells and DNA.

INTRODUCTION TO CANCER SCREENING AND TUMOR MARKERS FOR EARLY CANCER DETECTION

Tumor markers have been used for decades in oncology. Tumor markers are biomarkers found in blood, urine, cerebrospinal fluid, or other body tissues that are elevated in association with cancer. Tumor markers can, in theory, be used for screening, diagnosis, staging, or disease monitoring. However, to date, many tumor markers have demonstrated poor accuracy and efficacy, particularly among the most prevalent cancers. To understand biomarkers and other tests employed for earlier detection of new or recurrent cancer, one needs to understand a number of epidemiologic concepts.[2] Simply defined, screening is the use of a test among individuals with a population risk for or higher probability of cancer in order to detect that cancer sooner (secondary prevention) or prevent its complications (tertiary prevention). Rarely, a screening test is used to prevent cancer (primary prevention), such as the Papanicolaou (Pap) test to find precancerous cellular changes in the cervix. When screening is used to monitor for cancer recurrence, the term surveillance is commonly used instead.

For screening to be efficacious, a number of conditions are necessary. The cancer should be an important cause of morbidity and mortality. A proven, safe, and acceptable test should exist to detect early-stage disease. The natural history of the cancer should be understood. The cancer should have a recognizable latent or early asymptomatic stage. In the absence of intervention, all or most cases in a preclinical phase should progress to a clinical phase. Pseudocancer, or even overdiagnosis of a benign cancer that would never progress, can be problematic in this situation. Safe and effective treatment must be available. Finally, the screening test should be

economically balanced in relation to the total expenditure on medical care.

Among patients with undiagnosed cancer, a number of screening biases must always be remembered. Volunteers for screening are often healthier. Screening is susceptible to lead-time bias, that is, simply advancing the time of cancer diagnosis without changing the ultimate outcome. Length bias allows screening to detect more protracted, slower cancers, than rapid, severe forms, which leads to better outcomes in screened-detected cases because cancers with a better prognosis are being detected through the very screening modality being studied. Finally, screening can overdiagnose, which means it can detect premalignant lesions or early invasive cancers that would have never required any medical intervention in the lifetime of the patient. The latter has resulted in an epidemic of prostate cancer and ductal carcinoma in situ, many of which may never have been symptomatic or lethal.

When evaluating the utility of screening, one must always consider the test's accuracy (or relative lack of error). Sensitivity indicates the ability of the test to identify correctly those who have cancer among the population with cancer (true-positives/[true-positives + false-negatives]), whereas specificity indicates the ability of the test to identify correctly those who do not have cancer among the population without cancer (true-negatives/[true-negatives + false positives]). No screening test can have 100% sensitivity and 100% specificity,

and in general for many cancer screens, sensitivity hovers in the 70% to 80% range with specificity slightly lower at approximately 60% to 70%.

Perhaps most vexing about screening for cancer is the paradox of cancer epidemiology: cancer in the aggregate over a lifetime is common, while at any one time one specific cancer is rare. That is, at any given time, cancer prevalence by specific type is low, and a single asymptomatic individual has a low risk of cancer. This is crucial to understanding the limitations of screening tests, since the positive predictive value (PPV) of a test (the number of cancers among all the positive tests, i.e., true-positives/[true-positives + false positives]) is directly tied to cancer prevalence in the screened population. The lower the prevalence, the lower the PPV. PPV has been very low among traditional tumor markers and has led to their failure as mass cancer screening tests. Among a number of traditional cancer biomarkers (Table 1), we will look at studies of men undergoing asymptomatic prostate cancer screening with prostate-specific antigen (PSA), and women with breast cancer in remission under surveillance with carcinoembryonic antigen (CEA), CA-15.3, and CA-27.9. Although these biomarkers have failed to demonstrate utility, we look ahead to improvements in the PPV with novel imaging techniques in high-risk populations and circulating DNA and tumor cells to identify at-risk patients with greater precision.

Prostate-Specific Antigen as an Example for New Diagnosis of Cancer

PSA (kallikrein-3 [KLK3]) is a glycoprotein secreted by epithelial cells of the prostate gland, and is elevated in prostate cancer as well as benign prostatic hypertrophy and prostatitis. Although prostate cancer is an important cause of morbidity and mortality, the PSA test, which is both safe and acceptable, has led to the diagnosis of more cancers at an

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KEY POINTS

- "Screening" is the use of a test to detect cancer sooner (secondary prevention) or prevent its complications (tertiary prevention) among individuals at high risk for cancer. When screening is offered for patients already diagnosed with cancer, the term "surveillance" should be used instead.
- Tumor markers, such as prostate-specific antigen, carcinoembryonic antigen, CA-15.3, and CA-27.29, have not demonstrated accuracy and efficacy in neither diagnosing prostate cancer nor detecting breast cancer relapse sooner than other screening tools.
- Mammography in women age 50 to 70 (even possibly starting at age 40) and colonoscopy in the healthy population over age 50 play an important role in the early detection of cancer and are part of recommended guidelines for cancer screening.
- For patients at high genetic or familial risk for cancer, the addition of breast MRI is recommended for women in their early to mid-20s and colonoscopy is recommended for individuals in adolescence to their mid-20s (based on specific mutation or family history). For patients with a previous or active smoking history, an annual low-dose CT scan can be considered starting in their 50s.
- Circulating tumor cells and circulating tumor DNA offer novel genomic approaches to detect cancer through liquid biopsies and early screening programs, and further studies establishing their clinical utility are now required.

TABLE 1. Tumor Markers Commonly Used for Screening or Surveillance

Biomarker	Cancers
Alpha-fetoprotein	Germ cell tumors and hepatocellular carcinoma
Beta-human chorionic gonadotropin	Choriocarcinoma and testicular cancer
Beta-2 microglobulin	Multiple myeloma, chronic lymphocytic leukemia, and some lymphomas
CA-125	Ovarian
CA-15.3, CA2-7.29	Breast
CA-19.9	Pancreas, gall bladder and bile duct, and gastric
CD20	Non-Hodgkin lymphoma
Calcitonin	Medullary thyroid
Carcinoembryonic antigen	Ovarian, cervix, breast, urinary tract, gastrointestinal, and lung
Lactate dehydrogenase	Germ cell tumors
Prostate-specific antigen	Prostate

early stage. In fact, the poorly defined natural history of the disease has simply led screening to detect pseudocancers that would never have been problematic in most men. The positive predictive value (PPV) of the PSA test has been estimated at 30%.[3] The large majority of men who test positive with PSA at over 4.0 ng/mL do not have clinical prostate cancer. Although zero to one man in 1,000 might not die because of PSA screening, 110 would be diagnosed and, if treated, placed at risk of substantial morbidity. Of this group, 29 would develop erectile dysfunction, 18 urinary incontinence, two a serious cardiovascular event, and one deep venous thrombosis or pulmonary embolism.[4] The U.S. Preventive Services Task Force (USPSTF) thus concludes "that there is moderate certainty that the benefits of PSA-based screening for prostate cancer do not outweigh the harms," and discourages the routine use of this test.[4] The American Society of Clinical Oncology (ASCO) and the American Cancer Society take a more temperate recommendation stating that "men who have at least a 10-year life expectancy should have an opportunity to make an informed decision with their health care provider about whether to be screened."[5,6]

Carcinoembryonic Antigen and Other Markers for Detection of Breast Cancer Recurrence

CEA is a set of highly related glycoproteins involved in cell adhesion and is elevated in adenocarcinomas of ovarian, cervical, colorectal, lung, urinary tract, and breast origin. Elevated levels of the cell surface antigens CA-15.3 and CA-27.29 can identify breast cancer recurrence and metastases before symptoms occur. Risk of relapse and mortality from breast cancer is high, these tests are cheap and acceptable, and the natural history of the cancer is well understood, therefore employing these markers seems logical. Moreover, since cancer surveillance involves patients with a high chance of recurrence, that is, high cancer prevalence, these tests have high positive predictive value (PPV) and should have utility. However, use of these markers has not translated to any survival benefit. In serial guidelines, most recently in 2007, ASCO stated that there is insufficient evidence regarding disease-free survival, overall survival, quality of life, toxicity, or cost-effectiveness to support the routine use of CA-15.3 and CA-27.29 in clinical practice.[7] However, a recent study suggested that the use of these markers to predict breast cancer relapse remains a common practice among oncologists.[8] Among oncologists, factors associated with this overuse of surveillance testing include providers who are older age, low provider self-efficacy, international medical graduates, and greater perceptions of ambiguity about survivorship care.[9] Patients who are more likely to be tested serially for these markers are younger at diagnosis, have advanced stage at diagnosis, and reside on the East or West Coast.[8]

IMAGING AS AN APPROACH TO SCREENING FOR CANCER

Screening for cancer using radiographic imaging has been available for decades, and multiple clinical studies having demonstrated its efficacy in specific instances. Despite the evidence for the role of imaging as part of an early cancer screening and surveillance program, debate continues about the specific timing and imaging modalities that provide the most benefit with least harm to general and high-risk populations. The three cancers with the best consensus for benefit from early cancer detection using imaging include breast cancer, colorectal cancer (CRC), and most recently, lung cancer.

Breast Cancer Imaging

General population. In 2014, over 235,000 new cases of breast cancer were diagnosed in the United States and over 40,000 deaths attributed to the disease.[1] Several guidelines exist for screening for early detection of breast cancer in the average-risk, asymptomatic general population. Breast self-examination starting in the third decade of life can be considered part of screening for breast cancer, although clinical breast examination by a health care provider every 3 years is essential. Some organizations discourage breast self-examination because of the risk for increased biopsies and lack of evidence of benefit. Women should be advised to report any breast changes to their health care provider.

Mammography plays a crucial role for early detection of breast cancer. Pace and Keating published an outstanding review that includes a systematic assessment of mammography benefits and risks.[10,11] Based on over 50 years of published evidence, they concluded that regular mammography screening reduces breast cancer mortality by 19% (nearly 15% for women in their 40s and 32% for women in their 60s).[10] However, the cumulative risk for false-positive results is extremely high at over 60% for a woman who receives 10 years of annual mammograms in her 40s to 50s, and this can lead to increased anxiety, biopsies, and medical expenses.[10,11] The starting age and frequency of mammography must be balanced with an individual's risk for breast cancer and an awareness of a high likelihood of false-positive findings.[10-13]

Mammography guidelines have been proposed by various organizations with clear overlap, but also clear distinctions. Each organization recommends at a minimum that women between the age of 50 and at least 70 should receive mammography at least every 2 years (with consideration of annual screens by some groups starting at age 40).[1,14-18] When discussing this topic with patients, Pace and Keating[10] suggest to highlight: (1) mammography is not a perfect screening test, (2) mammography saves lives (five of 10,000 women age 40 to 49, 10 of 10,000 women age 50 to 59, and 42 of 10,000 women age 60 to 69), (3) mammography can overdiagnose and there is potential for false-positives (at least half of women undergoing annual mammography will be incorrectly told they might have cancer over 10 years, and 20% will require biopsy to prove it is not cancer), and (4) informed decision should rely on family history, individual risk, preferences, and expert recommendations.

High-risk populations (hereditary breast and/or ovarian cancer). Lifetime risk for breast cancer for women with hereditary breast and/or ovarian cancer (HBOC) syndrome (*BRCA1/BRCA2* germ-line mutations) approaches 40% to 65%, and some women are diagnosed as early as in their 20s. Recommended screening includes mammography plus breast MRI.[19,20] Compared with mammography, breast MRI offers better visualization of denser breast tissue often found in younger women.[21-24] In addition, exposure to mammography before the age 30 has been associated with increased risk for breast cancer in women with *BRCA1/BRCA2* mutations.[25] Mammography plus breast MRI in women who are *BRCA1/BRCA2* carriers offers comparable survival benefit with prophylactic bilateral mastectomy at age 25 and prophylactic bilateral salpingo-oophorectomy at age 40.[26] Sensitivity, metastasis-free survival, and overall survival was higher in patients with familial breast cancer treated with MRI compared with mammography-based screening for invasive cancer, but not ductal carcinoma in situ.[27] Many guidelines now suggest performing an annual MRI at age 25 and then alternating with digital mammography beginning at age 30 so that imaging of the breasts occurs every 6 months.[16,28]

Colorectal Cancer Imaging

General population. In 2014, nearly 140,000 new CRC cases were estimated to be diagnosed in the United States and over 50,000 deaths were attributed to the disease. Early CRC detection is known to improve clinical outcomes with multiple iterations of surveillance trials throughout the past 4 decades. Adenomatous polyps represent precursors to CRC, and the National Polyp Study in 1978 demonstrated that their removal dramatically reduces CRC risk.[29-31] Winawer et al later showed in a randomized clinical trial that colonoscopy 3 years after polyp removal was as effective as annual colonoscopy and urged a 3-year interval before colonoscopy after adenomatous polyp removal.[29] In more recent years, multiple population-based studies using case control, cross-sectional, and cohort designs have demonstrated that CRC risk and mortality are substantially reduced with regular colonoscopy screenings with odds ratios and standardized mortality ratio ranging from 0.23 to 0.71.[32-38] Additionally, the protective effects of screening using colonoscopy was noted to be more pronounced in the distal versus proximal colon.[32-34,36-39] U.S. gastroenterologists now offer screening in the general population at 5-year intervals beginning at age 50 and have begun discussing whether 10-year intervals could be effective.[32,40] The U.S. Multi-Society Task Force on CRC recently updated their guidelines to recommend 10-year intervals for surveillance after negative screening in individuals at average CRC risk.[41] The National Comprehensive Cancer Network (NCCN) recommends screening for CRC at age 50 if the patient has no family history of CRC and no personal history of adenoma or sessile serrated polyps (SSP), CRC, or inflammatory bowel disease.[42] NCCN guidelines suggest screening for CRC using colonoscopy, stool-based guaiac/immunochemical testing, or flexible sigmoidoscopy.[42] If no polyps or hyperplastic/non-SSP smaller than 1 cm are detected at colonoscopy, then rescreening with any modality is recommended in 10 years. If sigmoidoscopy is negative, then rescreening with any modality is recommended in 5 years. If adenoma/SSP is detected, then depending on number, size, and completeness of resection, repeat colonoscopy may be required every 2 to 6 months, 3 years, or 5 years. Results from the first two CRC screening examinations predict future CRC risks.[43] Despite the widespread adoption of colonoscopy for CRC screening, Samadder et al recently described in a population-based study that 6% of all patients with CRC still developed interval tumors within 6 to 60 months of colonoscopy (associated with higher rate of adenomas and CRC family history).[44] Three current randomized clinical trials in Europe and the United States are now investigating screening for CRC using colonoscopy and comparing colonoscopy with fecal immunochemical testing (or no screen) with 10- to 15-year CRC mortality. The reader is referred to the following consensus update by the U.S. Multi-Society Task Force on CRC[41] and in-depth review article[32] for excellent summaries of recent trials and discussions of CRC surveillance.

High-risk population (hereditary CRC syndromes). Patients at risk for hereditary CRC benefit the most from a rigorous screening program for early detection and polyp removal. Samadder et al offer an in-depth discussion about the evidence for screening for CRC in patients at high risk.[45] Specific recommendations are based on the CRC lifetime risk and earliest age of presentation unique to each syndrome. The NCCN offers excellent guidance on this topic organized by specific mutations.[42,46] For *MLH1* or *MSH2* mutations (Lynch syndrome/hereditary nonpolyposis colorectal cancer [HNPCC]), colonoscopy is recommended every 1 to 2 years beginning at age 20 to 25, or 2 to 5 years before the earliest colon cancer diagnosis before age 25. For *MSH6* or *PMS2* mutations (Lynch syndrome/HNPCC), colonoscopy is recommended every 1 to 2 years beginning at age 25 to 30, or 2 to 5 years before earliest colon cancer diagnosis before age 30. For an *APC* mutation resulting in familial adenomatous polyposis (FAP), if no symptoms are present, flexible sigmoidoscopy or colonoscopy every 12 months beginning at age 10 to 15 with consideration of prophylactic colectomy once the patient reaches an adult age. For an *APC* mutation resulting in attenuated FAP, colonoscopy is recommended during the late teen years, then every 2 to 3 years (Samadder et al suggest starting later at age 20 to 25). For *MUTYH* mutation (MUTYH-associated polyposis [MAP]), colonoscopy and polypectomy is recommended every 1 to 2 years, starting at younger than age 21 if there is a small adenoma burden. For *STK11* mutations (Peutz-Jeghers syndrome), colonoscopy and upper endoscopy is recommended every 2 to 3 years starting in the late teens (risk for stomach cancer is nearly 30%). For *SMAD4* mutations (juvenile polyposis syndrome), colonoscopy starting at approximately age 15 is recommended and should be continued annually if polyps are detected or every 2 to 3 years if no polyps are identified, with the same strategy for upper endoscopy (risk for stomach cancer is over 20% if multiple polyps are present).

Lung Cancer Imaging

High-risk smoking population. In 2014, more than 224,000 people in the United States were diagnosed with lung cancer and almost 160,000 patients died from lung cancer, making it the deadliest adult cancer. As imaging technology has advanced, so too has lung cancer screening and early detection using annual low-dose CT (LDCT),[47] which has led to both controversy and excitement in the field of early cancer detection. The National Lung Screening Trial (NLST) is the largest randomized clinical trial to be published. It demonstrated a 20% reduction in death in current or former smokers.[48,49] Six other lung cancer screening trials have been published or are ongoing.[50-56] Several recent reviews and editorials, as well as the current screening guidelines, summarize the benefits and harms associated with LDCT.[47,57-60] Similar to breast cancer and CRC, several professional societies have offered overlapping, but still distinct, recommendations and guidelines on screening for lung cancer (USPSTF,[61] American College of Chest Physicians/American Society of Clinical Oncology,[62] American Association of Thoracic Surgeons,[63] NCCN,[64] American Cancer Society,[65] and American Lung Association).[66] The majority of these organization recommend annual LDCT for high-risk individuals, which includes patients who are age 55 to 79 with a more than 30 pack-year smoking history, former smokers who have quit within the past 15 years, or patients age 50 to 79 with more than a 20 pack-year smoking history who have additional risk factors. Many cost-effectiveness analyses are being modeled for the national adoption of LDCT as the preferred method of screening for lung cancer in current or former smokers. In one study, the heath care expenditures were estimated to reach $1.3 to $2 billion with 50% to 75% screening uptake and $240,000 in additional costs to avoid one cancer death.[67] The authors argue that LDCT will prevent over 8,000 annual deaths from lung cancer, but they, and others, recognize that careful cost-effectiveness analyses will be key to understanding the true value of screening for lung cancer.[67,68] Nevertheless, the Centers for Medicare & Medicaid Services (CMS) recently announced that Medicare will cover LDCT in current or previous smokers, a move strongly supported by the American Lung Association. Similar to breast cancer, informed decision making—with understanding of the high likelihood for false-positives (one in five LDCT screening examinations may detect false-positive results, with each LDCT test 20 times more likely to yield a false-positive result than an actual lung cancer)—is key to initiating a lung cancer screening program.[58,69] Although LDCT now plays a more accepted and arguably standard role in the early detection of lung cancer, the best prevention is still to encourage smoking cessation.

CIRCULATING DNA AND CIRCULATING TUMOR CELLS IN CANCER SCREENING

Recent major advances in our ability to detect and characterize CTCs and cancer-specific (mutated) cell-free, circulating tumor DNA (ctDNA) have introduced the possibility of utilizing either or both as tests to screen for cancer. Particularly attractive is the possibility of simultaneous screening for multiple primary cancers, including tumor types for which no early detection method is currently available. Such a test should also prove complementary to any current standard organ-specific screening tests. Importantly, each of the current tests has multiple limitations, and poor compliance is a consistent challenge as a result of the unpleasant and/or invasive nature of many investigations. However, many obstacles must be overcome before a blood-based screening test, incorporating either CTCs or ctDNA, is proven to make a valuable contribution to early cancer diagnosis.

Liquid Biopsy in the Advanced Disease and Minimal Residual Disease Setting

Both CTCs and ctDNA are yet to be used in routine clinical practice. A major advantage of using CTCs in the management of cancer is that tumor cells can be isolated, which allows for morphologic identification and molecular characterization,[70] whereas ctDNA analysis is currently limited to mutation detection.[71] In advanced disease, both have demonstrated prognostic significance in multiple tumor types,[71-74] and initial changes in marker levels on therapy also provides an early indicator of treatment response.[73-76] Serial CTC and ctDNA analysis during therapy can also inform treatment resistance, including ctDNA-based detection of emerging mutations under the selective pressure of targeted therapies.[71] In the context of minimal residual disease, recent larger studies using CellSearch have found no or limited prognostic significance of CTCs across multiple tumor types.[74,77-79] In contrast, emerging data from studies of ctDNA for CRC[80] and breast cancer[81] indicate that ctDNA detected after definitive therapy for early-stage disease has powerful prognostic significance.

Potential Role for CTCs and ctDNA in Cancer Screening

Specificity. The specificity of any cancer screening test is of critical importance, as false-positive tests create patient anxiety and lead to further investigation with associated financial cost and morbidity. Studies of the U.S. Food and Drug Administration (FDA)–approved CTC testing platform, CellSearch by Veridex, indicate limited specificity with CTCs detectable in 4% to 15% of controls that either have no evidence of disease or benign conditions.[78] Many groups have recently reported improvements in the methods for detection, isolation, and characterization of CTCs that promise greater yield and improved specificity.

The early promise is that ctDNA should be a highly specific test,[71] because mutant DNA appears to be only released into the circulation, via apoptosis or necrosis, once there is an invasive tumor. In addition, and most relevant to the context of screening, more than one mutation should be detected for most tumor types of interest, with two false-positives an exceedingly unlikely finding. For the patient in whom only a single mutation is detected, the ability to readily repeat testing to confirm a positive result is advantageous. A repeat test

could also include an extended panel informed by the initial positive result. For example, where the initial panel reveals a mutated *RAS*, further testing might reveal an *APC* mutation in the circulation of the individual being screened. Detecting this *APC* mutation would provide reassurance that the initial screening result was a true positive, but also indicates the primary source is likely to be a CRC.

Sensitivity. When CTCs are assayed utilizing CellSearch, they can only be detected in about half of advanced cancers, and detection rates in patients with early-stage malignancy are no higher than in people without cancer. ctDNA provides a more sensitive marker since it is present in over 80% of advanced cancers, including in many patients in whom CTCs are not detectable.[71] The approximate 50-fold yield for ctDNA also provides a far greater dynamic range to assess changes over time. Most relevant to screening, ctDNA appears to be detectable in 73%, 57%, 48%, and 50% of early-stage colorectal, gastroesophageal, pancreatic, and breast cancers, respectively, including in 47% of patients with stage I tumors and increasing to 55% and 69% for stage II and III disease.[71] Other groups have also reported high detection rates in small series of patients with early-stage non–small cell lung cancer[81] and breast cancer.[82]

Optimizing and Tailoring the ctDNA Screening Panel

Unlike studies of ctDNA in patients with a known and characterized cancer, screening for an occult cancer will require an extended panel that covers the hotspots of genes frequently mutated in common cancers. The concept and feasibility of such a panel were demonstrated in a recent series in which liquid-based Pap smears were examined for somatic mutations known to accumulate in the cervix after shedding from endometrial or ovarian cancers.[83] A prototype test based on 12 frequently mutated genes in these tumors identified between one and five mutations in all 14 samples from patients with known cancer but unknown molecular profile (12 endometrial cancers, two ovarian cancers). No mutations were identified in samples from 14 women without cancer.

A panel of ctDNA mutations could be defined that would screen for the cancers of most interest in the general community population. Alternatively, a customized panel could be defined for particularly high-risk groups, such as hereditary syndromes. For example, a panel for patients with Lynch syndrome would include screening for gene mutations common in CRC and endometrial cancer. For any screening population, overlapping mutation profiles would mean that patients with any specific mutation would be screened for multiple cancers, including common *RAS* mutations in the HNPCC panel, which complements screening for CRC using colonoscopy and screening for pancreatic cancer.

Determining Further Investigation

Although ctDNA-based testing is attractive given the broad range of cancers that could be screened for using a single test, this advantage comes with a challenge— determining the source of a positive test. Medical oncologists are familiar with tissue-of-origin molecular profiling, which has an important role in the diagnosis of cancers of unknown primary. For a patient with a positive ctDNA result, a search for a primary tumor is also required, albeit with very different goals.

When ctDNA is detected, further investigation could be guided by the type of mutation(s) found, cancer risk factors, and the relative incidence of each cancer type. Smoking history would indicate an increased yield from lung imaging, and a family history or genetic syndrome would also suggest likely primary sites. Although $BRAF^{V600E}$ mutations are uncommon in CRC (present in approximately 8% of tumors) and ubiquitous in hairy cell leukemia,[83] this mutation is more likely associated with CRC as a result of the relative incidence of the two malignancies.

Alternate search strategies can be envisaged that should prove complementary to an organ-specific approach. CTC analysis should prove increasingly useful with the anticipated improvements in technology, potentially providing further confirmation of a true-positive ctDNA result. CTC detection would also provide opportunity for further characterization of the detected cells, which could guide the hunt for the primary site. Alternatively, whole body imaging, structural and/or functional, may prove to be a viable alternative to an organ-by-organ approach, given the high pretest probability. However, with each new investigation there is discomfort, cost, and the possibility of a false-positive result, therefore the value of each test needs to be carefully defined in prospective studies.

Combining ctDNA with Current Screening Modalities

The most exciting application of ctDNA is creation of a viable screen for many cancers for which no method of early detection is currently available. For tumors such as CRC or breast cancer, ctDNA-based testing should be complementary to the current screening modalities, as each test has a miss rate and is challenged by limited uptake. Importantly, for the 50% or more of patients who fail to comply with colonoscopic screening or the 30% or so who do not undergo regular mammography, it could provide an acceptable initial screening option. ctDNA testing could also prove helpful in characterizing indeterminate findings from routine screening tests, such as small lung lesions found using a screening CT scan in a patient who is a smoker.

OTHER ctDNA CONSIDERATIONS AND CONCLUSIONS

Although stage at diagnosis is the dominant prognostic factor for malignancies, the early diagnosis of a particular cancer type does not necessarily lead to higher rates of cure, and potential risks include overdiagnosis and/or overtreatment of cancers. It is presumed that for each primary cancer there will be a typical window from the point at which ctDNA is initially detectable to when the lesion is incurable, a window that may be only a few months or may be several years, and potentially may vary widely within a particular cancer type. There is much still to be learned.

A multitude of blood-based biomarkers have previously been proposed as cancer screening tests, but none have yet proven to be clinically useful, demonstrating the many challenges of translating initially promising data to a clinical reality. ctDNA-based cancer screening tests would appear feasible, given the available data regarding sensitivity and specificity. From here, carefully conducted clinical studies are required to determine the risks and benefits of early diagnosis across a broad range of tumor types, the optimal frequency of testing, the most desired ctDNA panel, the most efficient algo-

rithms for further investigation of any positive test, and the patient populations that will benefit most from screening.

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CANCER PREVENTION, GENETICS,
AND EPIDEMIOLOGY

Integrative Cancer Prevention: Nutrition, Supplements, and Lifestyle

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Can Diet and Lifestyle Prevent Breast Cancer: What Is the Evidence?

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OVERVIEW

Breast cancer is the most common cancer among women in both developed and less-developed countries. Rates of breast cancer are increasing worldwide, with a particular increase in postmenopausal and estrogen receptor-positive cases. The World Cancer Research Fund (WCRF) and American Cancer Society (ACS) cancer prevention guidelines recommend maintaining a healthy weight, undertaking at least 150 minutes of moderate intensity exercise per week, limiting alcohol consumption, and eating a plant-based diet. Observational data link adherence to physical activity and alcohol guidelines throughout life to a reduced risk of developing pre- and postmenopausal breast cancer. Weight control throughout life appears to prevent cases after menopause. Adherence to a healthy dietary pattern does not have specific effects on breast cancer risk but remains important as it reduces the risk for other common diseases, such as cardiovascular disease (CVD), diabetes, and dementia. Emerging data suggest that smoking during adolescence or early adulthood increases later risk of breast cancer. Lifestyle factors appear to modify risk among high-risk women with a family history and those with typical risk of the general population, although their effects among carriers of *BRCA* mutations are not well defined. Recent expert reports estimate that successful lifestyle changes could prevent 25% to 30% of cases of breast cancer. These reductions will only be achieved if we can implement targeted prevention programs for high-risk women and women in population-based breast screening programs during childhood, adolescence, and early adulthood when the rapidly developing breast is particularly susceptible to carcinogenesis.

Breast cancer is the most common cancer among women in both developed and less-developed countries, with an estimated 1.67 million new cases diagnosed worldwide in 2012 (25% of all cancers).[1] Breast cancer is a major cause of mortality in both developed (198,000 deaths, 15.4% of total; ranking second after lung cancer) and less-developed (324,000 deaths, 14.3% of total; ranking first) countries.

Incidence rates vary nearly fourfold among different regions of the world, with age-standardized rates of 29 to 36 per 100,000 in Asia and Africa compared with 91 to 96 per 100,000 in North America and Western Europe. These rates reflect differences in reproductive factors (late age of first pregnancy, fewer pregnancies, short or no breast-feeding, early menarche, late menopause) and lifestyle risk factors (obesity, inactivity, alcohol, Western-style diet, and use of hormone replacement therapy [HRT]).

More developed countries typically have fivefold higher rates of postmenopausal cancer than less developed countries (approximately 308 vs. 65 per 100,000), and twofold higher rates of premenopausal cases (29 vs. 13 per 100,000).[2] Global trends for the accumulation of risk factors are particularly associated with postmenopausal breast cancer. In the West, rates of estrogen receptor (ER)-positive cancers are increasing whereas those of ER-negative cancers are decreasing in all age, racial, and ethnic groups, and it is likely that global rates will follow these trends.[3,4]

Prevention of breast cancer must target both ER-positive and ER-negative subgroups and will be best achieved through preventive therapies for high-risk groups and lifestyle changes across all risk strata. Trends for an association between ER-positive breast cancer and a Western lifestyle suggest that this subtype may be particularly amenable to lifestyle prevention. Selective estrogen receptor modulators (SERMs) and aromatase inhibitors can prevent 50% to 80% of ER-positive breast cancers[5]; however, availability and uptake of these prevention therapies is currently low (1 to 40%, reviewed in Donnelley et al[6]). Despite apparent reductions in the rate of ER-negative cancer, its poor prognosis and high burden of breast cancer mortality make this subtype a priority for prevention. There are several promising, but as yet unproven, preventative agents for ER-negative cancer, including inhibitors of ErbB receptor, COX-2, or poly (ADP-ribose) polymerase, metformin, retinoids, and statins.[7]

This article summarizes current cancer prevention guidelines and current evidence for the links between diet and life-

style factors and breast cancer risk. We will present the sum of evidence of any specific links with pre- and postmenopausal breast cancer, ER-positive and ER-negative disease, and among women with familial risk, including those with the high-risk *BRCA1* and *BRCA2* breast cancer susceptibility genes.

CANCER PREVENTION GUIDELINES

The World Cancer Research Fund/American Institute for Cancer Research (2007) and the ACS (2012) have produced guidelines for prevention of a range of cancers that focus on weight control, regular exercise, reduced alcohol consumption, and a plant-based diet (Table 1). These guidelines are mainly informed by large cohort studies (i.e., prospective studies of 20,000 to 40,000 unaffected individuals), but also include some limited randomized data. Cohort studies include less recall and selection bias than case control studies; however, they can only highlight associations between lifestyle behaviors and cancer risk and cannot provide definitive proof of their role in cancer etiology. Healthy lifestyle behaviors tend to cluster, thus someone who eats a healthy diet is often a healthy weight, exercises regularly, has a moderate alcohol intake, and does not smoke. Researchers attempt to adjust for other confounding risk factors in analyses but residual confounding cannot be ruled out.

Defining the true anticancer effects of lifestyle choices without confounding factors can only be achieved through randomized controlled trials. Such trials would need to be large (approximately 26,000 to 36,000 patients) and are therefore potentially prohibitively expensive.[6] Testing

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KEY POINTS

- Breast cancer is the most common cancer in women in both developed and less-developed countries. Rates of breast cancer are increasing worldwide, with particular increases in postmenopausal breast cancer and estrogen receptor-positive disease.
- Overweight, obesity, and weight gain are linked to postmenopausal breast cancer, whereas alcohol consumption and lack of exercise increase the risk for both pre- and postmenopausal breast cancer.
- Rapid height growth or exposure to smoking and alcohol in the period between menarche and first pregnancy may increase risk because the rapidly developing breast is particularly susceptible to carcinogenesis.
- Adherence to a healthy dietary pattern does not have specific effects on breast cancer risk but remains important for women because it reduces the risk of other common diseases, such as cardiovascular disease, diabetes, and dementia.
- Excess weight, alcohol, and lack of exercise increase risk among women with a family history, but their specific associations with carriers of *BRCA1* and *BRCA2* mutations requires further study.

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whether lifestyle interventions can prevent breast cancer is a bigger challenge than investigating their effects on CVD because cancer does not have the well-defined surrogate endpoints available for CVD such as cholesterol and blood pressure. The absence of good markers for breast cancer risk makes it unlikely that randomized data will be available to support or refute cancer prevention recommendations in the near future.

So what is the evidence that general cancer prevention guidelines can prevent breast cancer? Several large cohort studies have reported lower rates of breast cancer among women who adhere to these guidelines. Five studies of postmenopausal women reported 16% to 60% risk reductions, mainly linked to reduced body fatness and alcohol intake rather than specific differences in dietary patterns.[8-11] In contrast, studies of a cohort of both pre- and postmenopausal women showed 31% lower rates of breast cancer in women who adhered to specific dietary recommendations of increased wholegrain products and reduced meat and alcohol, rather than other lifestyle factors.[12] Adherence to cancer prevention guidelines have been reported to reduce risk among women with and without a family history of breast cancer[9,13] and to reduce the risk for both ER-positive and ER-negative breast cancers.[8,11]

WEIGHT, WEIGHT GAIN, AND WEIGHT LOSS

Cohort studies consistently link overweight, obesity, and adult weight gain to risk for postmenopausal breast cancer. Women who gain 20 kg or more during adulthood double their breast cancer risk.[14] These gains are also associated with large increases in the risk for diabetes (12-fold),[15] CVD (threefold),[16] and colorectal cancer (1.5-fold).[17] Modest weight loss (5 to 10%) reduces risk. In the Iowa Women's Health Study of 34,000 women, a weight loss of at least 5% either before or after menopause reduced the risk for breast cancer by 25% to 40% compared to women who continued to gain weight, whereas Eliassen et al. reported a 50% reduction in risk in women with a 10% weight loss compared with weight-stable women in the Nurse's Health Study of 37,000 women.[18] Excess weight is mainly linked to the risk of developing ER-positive and ER-negative breast cancer after menopause and appears to be a factor among women with and without a family history.[14,19,20]

ALCOHOL

Consumption of an additional 10 g of alcohol (1 unit; e.g., 284 mL of 4% strength beer or cider, 25 mL of 40% strength spirits, or 80 mL of 12% strength wine) on a daily basis is estimated to increase risk by 2% to 12%,[20] with no further increase beyond 60 g of alcohol per day.[21] The increased risk is thought to be related to acetaldehyde-induced DNA strand deletions, chromosomal aberrations, and DNA adducts, downregulation of the tumor suppressor gene *BRCA1*, and increased estrogen and prolactin receptor activity. Data sug-

TABLE 1. World Cancer Research Fund Prevention Guidelines for Breast Cancer and Cardiovascular Disease

	Breast Cancer Risk Reduction	CVD Risk Reduction
1. Be as lean as possible without becoming underweight	√√	√√
2. Be physically active for at least 30 minutes every day	√√	√√
3. Avoid sugary drinks and limit consumption of energy-dense foods	√√ (to achieve weight control)	√√ (to achieve weight control)
4. Eat more vegetables, fruits	No effect	√√
5. Eat more whole grains and legumes such as beans	√√	√√
6. Limit red meats (i.e., beef, pork, and lamb) and avoid processed meats	Modest effect with processed meat √√	√√
7. Limit alcoholic drinks to 2 for men and 1 for women per day	√√	Lowest risk of coronary heart disease 1-2 drinks/day Stroke < 1 drink/day (40)
8. Limit consumption of salty foods and foods processed with salt	No effect	√√
9. Do not use nutritional or vitamin supplements to reduce risk of disease	√√√	√√√

Abbreviation: CVD, cardiovascular disease.
√√√ = Supported by meta analyses of randomized trials or one or more randomized trials.
√√ = Association in three or more observational studies.
√ = Association in one or two observational studies.

gest that alcohol intake before the first term of pregnancy is particularly associated with cumulative risk.[20] Unresolved questions include the specific effects of binge drinking, whether dietary folate intake can reduce the excess risk of higher alcohol intake, and interactions with genes involved in alcohol metabolism/detoxification and folate metabolism.[22] Light drinking (10 g/day) is also linked to breast cancer risk; however, zero alcohol intake is not recommended because light drinking is consistently linked to reductions in overall (17%)[23] and cardiovascular (20%)[24] mortality.

Alcohol increases risk of breast cancer among both pre- and postmenopausal women and for both ER-positive and ER-negative disease. Studies have suggested that alcohol affects risk equally or to a greater extent among women with a family history (defined as an affected first-degree relative) compared to women with no family history.[20]

PHYSICAL ACTIVITY

The American College of Sports Medicine recommends a total of 150 minutes per week of moderate intensity cardiorespiratory exercise to reduce all-cause mortality and improve quality of life.[25] The optimal level of physical activity for breast cancer risk reduction appears to be greater than these recommendations, with an estimated 3% reduction in risk for every additional 180 minutes of moderate intensity exercise per week.[26] Physical activity is associated with reduced risk among pre- and postmenopausal women and among women with a family history, albeit with an apparent smaller effect than for the general population, and reduced risk of both ER-positive and ER-negative cancers.[27] Potential anticancer effects of physical activity include reductions in endogenous sex hormone concentrations, insulin resistance, and chronic low-grade inflammation. In addition, other pathways are emerging as potentially important, including those involving oxidative stress and telomere length, global DNA hypomethylation, immune function,[28] and

increased gene expression of *BRCA* and other DNA repair genes. Although being "fit but fat" appears to protect against heart disease,[29] this is not the case for breast cancer, in which cancer protective effects of exercise are mainly seen in women who are a healthy weight and not among the overweight and obese.[26]

DIETARY FACTORS AND BREAST CANCER RISK

If a women is a healthy weight, exercises regularly, and moderates her alcohol intake does the actual composition of her diet matter?

Fruit, Vegetables, and Fiber

The 5-a-day campaign was launched in the United States in 1991 by the National Cancer Institute and the Produce for Better Health Foundation with the aim of preventing cancer. Since these initial campaigns, emerging evidence has consistently linked fruit and vegetable intake, particularly vegetable intake, to reduced overall and cardiovascular mortality but not specifically to cancer mortality.[30] The WCRF Continuous Update Project recently stated there is no convincing evidence that fruits and vegetables play a role in the etiology of colorectal, breast, and pancreatic cancers.[31]

Recent systematic reviews have linked higher fiber intake with a lower risk of breast cancer, with a 5% risk reduction for every additional 10 g of fiber per day. Fiber may reduce risk by reducing the reabsorption of estrogen and androgens in the bowel and hence their circulating levels. Soluble fiber appears to be the most protective, possibly through its beneficial effects on insulin sensitivity.[32]

Meat, Fish, and Dairy Foods

Vegetarian or vegan diets do not specifically reduce risk. Women with a higher consumption of meat are at slightly increased risk; each additional 100 g of red meat per day increases risk by 4% (relative risk [RR] 1.04 [1.00 to 1.07]) and

each additional 30 g of processed meat per day increases the risk by 3% (RR 1.03 [1.00 to 1.06]).[33,34] It is not clear why meat has this effect. Risk of breast cancer does not appear to be related to its saturated fat or carcinogenic heterocyclic amine content. Heterocyclic amines are also found in poultry and fish, which respectively have neutral and protective effects on breast cancer risk. It is possible that meat may be an innocent bystander in these studies, and a marker of an overall unhealthy lifestyle.[33,34] Marine omega-3 fats, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are associated with reduced breast cancer risk; each additional 0.7 g of marine omega-3 polyunsaturated fat per week reduces risk by 5%. Two portions of oily fish per week provide 3.5 g of n-3 fatty acids and a potential 25% risk reduction; however, the vegetarian n-3 fat alpha-linolenic acid does not reduce risk.[35]

Dairy foods are perceived to be a cause of breast cancer by many populist websites and patient advocacy groups as they contain the potentially cancer promoting hormones estrogen and insulin like growth factor.[36] These concerns are not supported by evidence. A recent meta-analyses including 1,063,471 participants and 24,187 cases found a 16% lower rate of breast cancer among high (> 3 servings/day) versus low (< 1 serving/day) dairy consumers. Risk reduction may be related to the content of calcium, conjugated linoleic acids, or vitamin D, which is found in fortified milk products.[37]

SOY FOODS AND ISOFLAVONES

Eight out of 10 breast cancers are estrogen dependent. Soy foods contain isoflavones, which have weak estrogenic and antiestrogenic effects in addition to nonhormonal effects that inhibit cancer cell growth in the laboratory. Not surprisingly, many studies have examined the links between soy and risk of breast cancer. A recent meta-analysis summarized 14 studies involving 369,934 participants and 5,828 cases of breast cancer. This study showed that women who consume moderate amounts of soy throughout their life have a lower breast cancer risk; intake of 5 g of soy protein/day (10 mg of isoflavone, equivalent to 170 mL of soy milk or 120 g of soy yoghurt) was associated with a 4% reduction in risk.[38] This effect was mainly seen within Asian, but not Western, populations, in postmenopausal versus premenopausal breast cancer and for both ER-positive and ER-negative cancers. Risk reduction may largely be related to the biologic effect of soy on the developing breast, which leads to a more differentiated breast phenotype in adulthood.[39] Hence, soy intake as a child or adolescent may be more important than its introduction to the adult diet. These data are based on intakes of soy food rather than over the counter isoflavone supplements. The effects of these supplements on breast cancer, or indeed on cholesterol lowering, have not been demonstrated.[40]

Healthy Dietary Patterns

Adherence to a Mediterranean diet (MD), which typically includes legumes, cereals, fruits/nuts, vegetables, extra-virgin olive oil, red wine in moderate quantities, and low amounts of red meat, poultry, and dairy products, is consistently linked to reductions in the risk of CVD, diabetes,[41] and dementia.[42] These reductions appear to be diet specific and independent of weight and other lifestyle risk factors. Adherence to a MD has been associated with significant reductions in the risk of overall (10%), colorectal (14%), and prostate (4%) cancer, but not specifically with breast cancer, even when alcohol intake is removed from the MD score (RR 1.01, 95% CI, 0.88 to 1.16, p = 0.89).[43] Energy balance and adiposity seem to be more important for preventing breasting cancer than the specific composition and quality of the diet. After a breast cancer diagnosis, adherence to a healthy diet is not linked to breast cancer mortality but is linked to reduced mortality from other causes.[44,45] Therefore, adherence to a healthy dietary pattern remains important for women at risk of breast cancer and women who have already been diagnosed, as both groups are at risk of developing other health conditions that are affected by diet.

Vitamin Supplements

One in three adults in the United States take vitamin supplements in the hope of protecting themselves against ill health and cancer. Large-scale randomized trials of supplement use have mainly yielded negative findings, with some notable adverse and beneficial effects. For example, beta-carotene increases the risk of lung and stomach cancer, vitamin E increases the risk of prostate cancer and colorectal adenoma, and selenium reduces the rates of gastric and lung cancer in populations with low selenium levels but increases rates in those with higher levels. Both beta-carotene and vitamin E supplementation increase overall mortality.[46] Supplementation with vitamin D,[47] calcium,[48] folic acid,[49] or multivitamins[50] neither decrease or increase the risk of breast cancer. The best advice is to avoid nutritional supplements unless indicated for a specific reason.

SMOKING

The 2004 Surgeon General Report concluded, "It would be false to tell women they will prevent breast cancer if they quit smoking." Accumulating evidence from the better-designed epidemiologic studies suggests an increased breast cancer risk among women with the highest exposure, i.e., the longest duration and highest pack years of smoking. The updated 2014 Surgeon General Report concluded that current evidence was suggestive, but not sufficient, to infer a causal relationship between active or passive smoking and breast cancer.[51] Smoking appears to have adverse effects if initiated during adolescence or early adulthood before the first pregnancy because of heightened susceptibility to chemical carcinogens before full differentiation of the breast. Smoking appears to have more consistent links with premenopausal breast cancer but has also been linked to postmenopausal breast cancer.[52,53] Multivariate adjusted relative risks between the highest exposure category and never active smok-

TABLE 2. Breast Cancer Prevention across the Life Course[66,67]

Timing of Exposure	Before Menarche		After Menarche and before First Birth		Premenopausal Years		Postmenopausal Years
Links to pre- or postmenopausal breast cancer	Pre	Post	Pre	Post	Pre	Post	Post
Greater adiposity	= or ↓	= or ↓	= or ↓	= or ↓	=	↑	↑
Height growth velocity	↑	↑	NA	NA	NA	NA	NA
Sedentary lifestyle	?	?	↑	↑	↑	↑	↑
High alcohol intake	NA	NA	↑	↑	↑	↑	↑
Smoking	?	?	↑	↑	=	=	=
High soy intake	↓	↓	↓	↓	=	=	=

Abbreviations: NA, not applicable; Pre, premenopausal breast cancer; Post, postmenopausal breast cancer.
= No effect.
↓ Decreased risk.
↑ Increased risk.

ers in positive cohort studies are between 1.1 and 1.4. The effect of smoking appears to be mainly linked to ER-positive cancers and among individuals with polymorphisms in genes involved in the metabolism of tobacco products, such as *NAT2*, although the current evidence is equivocal.[52]

LIFESTYLE MODIFICATION OF RISK AMONG *BRCA1* AND *BRCA2* CARRIERS

Rates of breast cancer have increased among high-risk populations with mutations in the *BRCA1* and *BRCA2* breast cancer susceptibility genes, mirroring the increase in rates among the general population over the last century. A published data set from Iceland reported a fourfold increase in the cumulative incidence of breast cancer (before age 70 years) between 1920 and 2000 among *BRCA2* carriers (18.6% to 71.9%) and women in the general population (1.8% to 7.5%).[54]

A marked increased penetrance of *BRCA* mutations over the years has been shown in a number of cohorts and is thought to reflect increased reproductive and lifestyle risk factors, although the exact causes remain unknown. High-quality large-scale genome-wide association studies have identified genetic variation in loci that affect *BRCA* penetrance. In contradistinction, modifiable risk factors have mainly been studied in small case-control studies with retrospective collection of lifestyle risk information, which are often confounded by ascertainment bias in clinic-based settings and survival bias, and the findings have not been validated in independent replication sets. These studies have produced equivocal evidence that risk among *BRCA1* and *BRCA2* carriers is increased with weight and smoking and

TABLE 3. What Causes Breast Cancer? The Mismatch between Expert Opinion and Lay Perception

Expert Opinion (Estimated Attributable Risk [U.K])[63]		Common Beliefs among Healthy Women (1,297 patients)[68]	
Non-modifiable	% of cases	Non-modifiable*	% citing this reason
Genetic factors**	47	Genetic factors	77.6
Reproductive factors: nulliparity, late parity, lack of breastfeeding[69]	11	Environmental pollutants	31.7
Occupational-shift work	4.6	Stress	27.9
Potentially modifiable factors	% of cases	Food additives	18.4
Obesity	9.0	Pesticides	10.0
Alcohol consumption	6.4	Food additives	18.4
Physical activity	3.4	Reproductive	7.2
Use of HRT	3.2	Breast injury	6.6
		Chance, fate/God's will	6.5
		Potentially modifiable factors	% citing this reason
		Diet	23.2
		Alcohol	12.6
		Physical activity	11.6
		Smoking	11.6
		Use of HRT	7.2

Abbreviations: HRT, hormone replacement therapy.
*Totals could exceed 100% as respondents could identify agents from multiple categories.
**DG Evans, personal communication, 2014.

TABLE 4. Current Evidence for Lifestyle and Breast Cancer Risk

	Overall Effect	Premenopausal	Postmenopausal	ER-positive	ER-negative	Family History	BRCA1	BRCA2
Weight and adiposity	√√	Mixed effects	√√	√√	√√	√√	* Mixed effects	* Mixed effects
Lack of exercise	√√	√√	√√	√√	√√	√√ Reduced effect cf non family history	* Mixed effects	* Mixed effects
Alcohol intake	√√	√√	√√	√√	√√	√√	* No links found	* No links found
Smoking during adolescence/early adulthood/lifelong smoking	√√	√√	√√	√√	Lack of data	No data	No data	No data

*Low-quality case-control data.
√√Association in three or more observational studies.
√Association in one or two observational studies.

reduced with physical activity (especially if undertaken during adolescence and early adulthood), with consistent null effects of alcohol.[55,56] The limitations of these studies are well recognized and large-scale prospective studies are required. Recent prospective data from a New York cohort showed that adherence to cancer prevention guidelines for a healthy weight, reduced alcohol, and high physical activity reduced breast cancer mortality by 61% (hazard ratio 0.39; 95% CI, 0.16 to 0.97) among *BRCA1* and *BRCA2* carriers.[57]

THE ROLE OF LIFESTYLE AND RISK REDUCTION IN THE GENOMIC ERA

Genome-wide association studies have identified more than 90 single nucleotide polymorphisms that are linked to breast cancer risk.[58] Gene–environment interactions are an area of increasing research interest with the potential to identify women for whom particular risk factors and/or lifestyle changes may be beneficial. There are few data on gene–environment interactions. An interaction between the *CASP8-rs1045485* polymorphism, which modifies breast cancer risk, and alcohol consumption has been replicated in a few datasets.[59]

LIFESTYLE PREVENTION OF BREAST CANCER ACROSS THE LIFE COURSE

Although 75% to 80% of breast cancer cases in Western cohorts occur after menopause, successful prevention of these cases, and the 20% to 25% that are premenopausal, must start earlier in life. Breast cancer risk can accumulate during childhood, adolescence, and particularly in the period between the menarche and first pregnancy before the breast cells become differentiated and less susceptible to carcinogenesis (Table 2). Rates of growth in childhood and excess alcohol and smoking in early adulthood increase risk, whereas soy intake during these years may reduce risk. Weight gain during pre- and postmenopausal years increases the risk of postmenopausal (but not premenopausal) breast cancer.[60,61] Breast cancer prevention interventions should therefore focus on preventing weight gain during the premenopausal years. Greater adiposity in childhood or early adulthood does not increase breast cancer risk, and can sometimes put women at lower risk. The reason for this weight paradox in breast cancer is not clear but most likely reflects the fact that heavier young women do not experience as much weight gain during adulthood, and it is adult weight gain that appears to put women at particularly high risk. Also, young overweight women have lower serum progesterone concentrations.[62]

HOW CAN WE ENGAGE WOMEN IN BREAST CANCER PREVENTION?

Recent expert reports estimate that successful lifestyle changes could prevent 25% to 30% of cases of breast cancer.[63] However, there is a general public skepticism about whether an individual's actions can influence whether they develop cancer. The most commonly cited perceived causes of breast cancer are mainly out of the individual's control, for example genetics, environmental pollutants, pesticides, and God's will (Table 3). Although many women who develop breast cancer have a genetic disposition, this is not the sole reason why they develop breast cancer; in most cases a complex interaction between genetic, reproductive, and lifestyle factors is involved.[54]

There is a need for consistent evidence-based cancer prevention messages that are supported by good mechanistic data to allow the public to understand and visualize the risk information they receive.[64] Current evidence-based messages are summarized in Table 4. These messages need to be backed up with effective programs to support adherence at key time points across the life course. There is increasing interest in whether women attending breast screening can be engaged in a healthy lifestyle to prevent breast cancer.[65] The overlap between lifestyle recommendations for preventing breast cancer and CVD (Table 1), as well as diabetes and dementia, may be exploited to develop prevention programs for multiple diseases in women.

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The author(s) indicated no potential conflicts of interest.

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CARE DELIVERY AND PRACTICE MANAGEMENT

Alternatives to ASP-Plus-Six: What Are the Options?

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Reform of the Buy-and-Bill System for Outpatient Chemotherapy Care Is Inevitable: Perspectives from an Economist, a Realpolitik, and an Oncologist

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OVERVIEW

Treating patients with cancer with infused or injected oncolytics is a core component of outpatient oncology practice. Currently, practices purchase drugs and then bill insurers, colloquially called "buy and bill." Reimbursement for these drugs is the largest source of gross revenue for oncology practices, and as the prices of cancer drugs have grown over time, these purchases have had significant impact on the financial health of practices and pose a risk that jeopardizes the ability of many practices to operate and provide patient care. Medicare Part B spending on drugs is under political scrutiny because of federal spending pressures, and the margin between buy and bill, lowered to 6% by the Medicare Modernization Act and further decreased to 4.3% by sequestration, is a convenient and popular target of budgetary discussions and proposals, scored to save billions of dollars over 10-year budget windows for each percentage-point reduction. Alternatives to the buy-and-bill system have been proposed to include invoice pricing, least costly alternative reimbursement, bundling of drugs into episode-of-care payments, shifting Part B drugs to the Medicare Part D benefit, and revision of the failed Competitive Acquisition Program. This article brings the perspectives of policy makers, health care economists, and providers together to discuss this major challenge in oncology payment reform.

Many alternatives to oncology's current buy-and-bill system for infused or injected oncolytics have been proposed. Although no single solution has been selected, reform of the system is inevitable. Here we present observations on the current system and its possible reform from the perspectives of an economist looking at the market forces inherent in average sales price (ASP)-based pricing, a realpolitik focusing on what is possible in a U.S. Congress fractured by ideology and partisanship, and an oncologist.

THE ECONOMIST

Treating patients with cancer with infused or injected anticancer prescription drugs (oncolytics) is a central component of an outpatient oncology practice. Practices purchase these drugs and then bill insurers for their use to treat specific patients, a system known as "buy and bill." Spending on these drugs by third-party payers is also increasingly important—Medicare spent approximately 5% ($125 billion) of the 2013 federal budget on the use of these drugs.[1]

From an economic perspective, reform of the buy-and-bill system is inevitable for two reasons. First, these purchases have had a substantial effect on practices' financial health and have created significant practice risk, jeopardizing many practices' abilities to operate and provide patient care in the community.[2] Second, there is widespread perception in policy circles that the system creates a perverse incentive for outpatient oncology practices to use more expensive oncolytics rather than pursuing more cost-effective treatment strategies. These incentives may also place upward pressure on the launch prices of new drugs. This section is a review of the economic rationales and extant supportive evidence underlying these drivers of reform.

An Overview of the Buy-and-Bill System

Fee-for-service (FFS) Medicare is the most prominent U.S. payer for oncolytics, followed by commercial insurers, and then state Medicaid programs. FFS Medicare pays for physician-administered oncolytics through the medical Part B benefit. By law, Medicare does not directly negotiate with drug manufacturers on the prices for prescription drugs covered under the Part B benefit, nor the oral oncolytics largely covered under Medicare's pharmacy Part D benefit. Section 1861 of the Social Security Act, which requires that the Medicare program cover reasonable and necessary medical services, precludes consideration of cost or cost-effectiveness in coverage decisions.[3] The Centers for Medicare & Medicaid Services (CMS) and commercial insurers rely on U.S. Food

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and Drug Administration approval and authoritative compendia to determine what uses of physician-administered drugs to reimburse, including "off-label uses determined by expert assessments of available supportive evidence."[4,5]

Currently, Medicare pays for Part B– covered drugs using an ASP of cancer drugs plus the 6% facilities/operations services fee reimbursement system, implemented in 2006 after the passage of the Medical Modernization Act (MMA) in 2003. ASPs for each Part B– covered drug are calculated and reported by pharmaceutical companies to CMS.[6] The MMA sets CMS' reimbursement for these drugs at ASP plus 6%, which preserved the buy-and-bill system while reducing the potentially substantial spread between Part B– covered drugs' acquisition costs and reimbursement rates. Medicare beneficiaries treated with these drugs are subject to a 20% coinsurance requirement, which is covered under secondary insurance plans for the majority of FFS Medicare beneficiaries.

The Challenges of Using ASP to Reimburse Outpatient Oncology Practices

Although ASP-based MMA reimbursement has led to some of the greatest reductions in Medicare Part B spending in its

KEY POINTS

- Reform of buy-and-bill chemotherapy is inevitable due to the financial risks it poses on practices and the widespread perception that it incentivizes increased utilization of the most expensive oncolytics.
- Challenges imposed by ASP-based reimbursement include underwater drugs, generic drug shortages, direction of underinsured and uninsured patients from private practice to more expensive hospital outpatient departments, and consolidation of oncologists into mega-practices and hospital employment.
- Although the U.S. Congress has not yet heeded regular calls for reductions in ASP plus 6% by presidential budgets and MedPAC, neither has it succeeded in removing prompt pay discounts from its calculation after 10 years of lobbying, and calls to fix the disproportionate impact of sequestration on oncology have been given only lip service by legislators.
- Though the failings of the buy-and-bill system impact all oncologists, small independent practices shoulder the greater burden, and their very existence, and with it access to care for many of our most vulnerable patients, is threatened.
- Oncologists are encouraged to be engaged and innovative in seeking alternative payment systems for buy-and-bill chemotherapy that will complement reforms of fee-for-service medicine. Possibilities include bundled payments, least costly alternative reimbursement, shifting Medicare Part B drugs into Medicare Part D, invoice pricing with management fees, government/payer-negotiated drug pricing, value-based payment formulas, and revamping the Competitive Acquisition Program.

history, several flaws in the methodology have become apparent to practitioners and policy makers.

First, CMS posts a new ASP every quarter based on information submitted by drug manufacturers 6 months earlier. As a consequence, drug prices commonly increase, whereas physician reimbursement remains stagnant because of the lag in ASP reimbursement policy.[7] This mismatch between acquisition costs and Medicare reimbursement for a particular drug can result in it being underwater (meaning the buy costs more than the bill) among providers—price increases are borne by outpatient practices until Medicare reimbursements catch up two quarters later.

Second, the lag in ASP-based reimbursement may have some perverse effects on the supply of generic oncolytics that commonly act as the backbones of chemotherapy with more novel agents. Once multiple manufacturers produce a given generic drug, competitive market forces drive their acquisition costs to levels that leave manufacturers very thin margins. If a generic drug manufacturer faces increases in the prices of raw material acquisition or costs of manufacturing and/or distribution, they may wish to pass these cost increases in whole or in part to drug purchasers. The lag in ASP reimbursement, however, forces generic manufacturers to assume all or some of the financial consequences of increased production costs for a defined period of time. Facing this option, generic manufacturers may opt to cease production of these drugs or outsource them to contract manufacturers. This may have contributed to ongoing generic cancer drug shortages.[8]

Third, reliance on ASP as the basis of outpatient oncology practice drug reimbursement has had heterogeneous and unequal effects across providers. On the bill side, practices can have substantially different payer mixes because of socioeconomic characteristics of their location. Commercial payers were slow to adopt ASP pricing and generally continue to reimburse more generously than Medicare, making practices that have richer, commercially insured patients less vulnerable to ASP and its changes.

On the buy side, ASP rewards practices enjoying substantial purchasing advantages that others do not immediately enjoy. For example, institutions that are eligible for 340B drug discounts access drugs at relatively low costs, insulating them from many of the financial pressures independent practices face.[9] When calculating ASP for purposes of Medicare reimbursement, regulations instruct manufacturers to exclude sales to 340B providers. Hence, Medicare reimbursement rates are not affected by growth in the 340B discount program, although providers' acquisition costs are reduced. Large group and institutional practices with lower drug-acquisition costs have a competitive advantage compared with smaller practices. Large practices typically have better access to capital and favorable commercial contracts compared with smaller practices, allowing them to more easily benefit from any spread between insurer reimbursements and the acquisition costs of drugs.

The risks and inequities in the ASP system have become exacerbated in recent years as the acquisition costs for newly launched Part B– covered oncolytics have increased expo-

nentially. Many small- to medium-size practices recognize that they cannot risk providing new, expensive therapeutics in the office. An entire clinic can be jeopardized by a failure to be wholly or partially reimbursed in a reasonable time frame for a given dose or cycle of an expensive drug. This is particularly problematic in rural and other underserved areas, where disadvantaged practices must seek size, capital, and management to survive.

Perceptions of Perverse Behavior in Response to Buy and Bill

There are several actors and associated behaviors that policy makers point to as being both related to buy and bill and symptomatic of its unintended consequences.

First, buy and bill sets up a system where oncologists who provide care to patients with cancer face financial incentives to administer intravenous anticancer drugs. In most industries, there is not much difference between wholesale and retail prices, and so they send consistent signals. But when wholesale and retail prices for drugs diverge systematically, incentives for dysfunctional behavior may be created. Oncologists and hospitals profit on the spread between the reimbursed price and the wholesale cost. Malin et al reported that many oncologists report that they face financial incentives to administer anticancer drugs.[10] Evidence also suggests oncologists' drug choices do appear to be responsive to profit margins (for examples, see Jacobson et al 2010 and Conti et al 2012), although there remains controversy about the quality of this evidence.[11,12]

On a related noted, a number of authors have also questioned whether some novel, high-cost chemotherapies are being used inappropriately in clinical practice related to the incentives in buy and bill.[13,14,15,16] The extent of inappropriate chemotherapy use is a public policy concern because of the cost and potential harms to patients from the use of toxic agents with little likelihood of clinical benefit.[17,18] It is important to note that the results of the most recent study suggest that physician-administered oncolytics are used off label with a frequency similar to other commonly used medication classes in the nononcology setting (20% to 50%).[19]

Second, on the buy side, downward pressure on reimbursement levels in buy and bill may incentivize outpatient practices to substantially shift the risks associated with the buy-and-bill system and/or to seek the lowest acquisition costs available for a given drug. A recent report suggested the share of physician-owned private practices in oncology decreased 10 percentage points between 2010 and 2011, and merger and acquisition activities between community oncology groups and hospitals and large provider groups have increased substantially. According to one estimate, between 2005 and 2011, the amount of chemotherapy infused in community doctor offices decreased from 87% to 67% even as the share of Medicare FFS payments for chemotherapy administered in hospitals (as opposed to outpatient oncology practices) increased from 16.2% to 41%.[20]

Furthermore, mergers between 340B providers and non-340B providers have substantially expanded the program's reach. One industry source (Biotechnology Industry Organi-

zation 2013) predicts that the volume of drug sales under the 340B program will increase from $6 billion in 2010 to $12 billion in 2016. This figure includes anticancer and non-cancer drugs. Industry sources indicate that the two therapeutic classes having the largest 340B sales are anticancer drugs and anti-infectives. These decisions influence the number of available oncology practices in a community, and places upward pressure on the prices paid for the provision of similar services.[21,22,23]

Finally, ASP-based reimbursement does not appear to curb the initial pricing of a branded cancer drug, most of which now meet or exceed $10,000 per month of treatment.

Howard and colleagues[24] reported that the launch prices of cancer drugs increased 9% to 17% between 1995 and 2012, after controlling for inflation. Because many rebates and discounts are based on a drug's average price, the expansion of rebate and/or discount availability presents pharmaceutical companies with an incentive to set higher list prices to offset discounts. In this way, increases in the number of 340B-eliglble providers may have led to upward pressure in the prices paid by noneligible providers.[24] This incentive likely acts to inflate the launch prices of new drugs, in part because manufacturers understand that practices may face substantial financial risk if drug prices increase after launch because of the lag in ASP-based reimbursement.

THE REALPOLITIK

It is an open secret in Washington, D.C., that when the Congress or the President are looking for substantial savings to pay for tax cuts or other spending priorities, they go to the Medicare program for the same reason that Willie Sutton robbed banks: that is where the money is. In an ideal world, savings would be achieved through careful consideration of the intended and un-intended consequences of the proposed policy reform, but that is not how the process usually works. Typically, a savings target (the amount of money needed to pay for other policy priorities) is established, and the policies that are most likely to be scored by the Congressional Budget Office to achieve this target are chosen. Formulas such as ASP and ASP plus are an ideal target for this type of approach because the math is straightforward. Combine simple math with a strong feeling by many health policy analysts and economists that ASP plus–based reimbursement creates perverse incentives for oncologists to preferentially choose drugs with the highest ASP to maximize revenue, and you have an irresistible target.

Although there are certainly members of Congress who are sympathetic to the havoc that would be created to the financial viability of oncology practices if ASP were to be eliminated, this sympathy has not led to a strong defense of cuts that have already gone into effect. As part of the 2012 budget sequester, Congress mandated CMS to cut Part B drug reimbursement by 2%—the result of which is that drugs are now paid at ASP plus 4.3%. Congress has had two subsequent opportunities to fix this problem with bipartisan budget agreements in November 2013 and November 2014, but not only did the problem go unfixed, Congress extended the cuts to

2024. Specific legislation, HR 1416, was introduced to fix this cut in the 113th Congress and never made it out of any of the three committees to which it was referred, despite having 124 cosponsors. In addition to lack of Congressional support, ASP reductions to ASP plus 3% have been part of the President's annual budget for the last several years. Finally, in a November 2014 hearing of the Medicare Payment Advisory Commission (MedPAC), the commissioners were in agreement that ASP policy creates a perverse incentive for providers to use more expensive medications rather than trying to control costs.

This leaves two choices for the oncology community: fight any further cuts to ASP and hope that we, as a community, have enough political clout to stop further cuts to ASP, or offer alternatives to ASP that shift our financial model from margins on drugs to one where we get paid to care for complicated medical patients. Receiving new budget allocations from Congress to do this is highly unlikely in the current environment. This means that money already in the system must be reapportioned. The ASP plus formula is not the only source of that revenue, but it is a logical one. However, we can only reapportion that money if it is actually in the system. If we wait too long, and ASP receives further cuts, then that is money we will never get back.

Recent proposals for the reform of outpatient oncology care, including the American Society of Clinical Oncology's (ASCO's) Consolidated Payments for Oncology and the Community Oncology Alliance's oncology medical home–based payment reform, have not received the serious attention that they should have garnered from policy makers, in part because they did not include a proposal for the direct reform of the outpatient chemotherapy administration reimbursement.

Freeing oncologists from dependency on drug revenues while keeping outpatient oncology viable requires a focus on reimbursement for services that are uncompensated or undercompensated in the current system. By seizing on the opportunity to participate in policy makers' active debate on the reform of the outpatient oncology reimbursement system, we can ensure the long-term sustainability of community-based outpatient oncology practice for current and future providers and patients.

THE ONCOLOGIST

At the core of cancer medicine is the delivery of oncolytic therapies and supportive care. For the medical oncologist this means pharmaceuticals, the majority of which are administered in hospitals and clinics. In contrast to oral medications, where direct physician ownership of pharmacy is largely prohibited, oncologists in private practice buy and bill the drugs that they then prescribe and administer. These drugs represent the largest single item expenditure and the largest source of gross revenue for these practices, and, until recently, the margin between purchase price and sale price was the financial driver of oncology infusion suites and oncologist incomes.[25] Similarly,

hospital- and institutionally-owned oncology clinics gain substantial revenues through outpatient administration of oncolytics, which contributes to the growth of hospital-based cancer programs.[20]

It would be naive to expect that the medical oncology community would be represented by a single sentiment or opinion about the buy-and-bill system. Varied sentiment may be shaped by physician experience and philosophic or political leanings, site of service, geography, and practice demographics. Likewise, it is naive to believe that payment reforms will impact only one sector of oncology. ASP-based pricing was developed initially for private practice oncology and Medicare, and now it permeates all oncology sites of practice and all payers.

Before the implementation of the MMA in 2003, chemotherapy was paid as a percentage of Average Wholesale Price (AWP). AWP was anything but average wholesale pricing, and it could better be characterized as a suggested retail price set by the manufacturer. Before MMA, there had been steady decreases in Medicare drug payments, and by 2003 Medicare paid AWP — 15%. The mechanics of the process, however, allowed manipulation of the system, and physician margins were commonly 30% to 50% of their purchase price and even sometimes up to 200% to 300% in well-publicized, isolated circumstances.[26]

With implementation of the MMA's ASP plus 6% drug reimbursement, the margin between buy and bill for Medicare patients substantially decreased for oncologists in private practices. The effect was initially buffered by Medicare demonstration projects, temporary increases in infusion fees, and relatively lucrative commercial contracts. However, over time Medicare discontinued the demonstration projects and allowed deadlines to permanently adjust infusion fees to fall by the wayside, and commercial payers, in efforts to combat escalating oncolytic drug prices, adopted ASP-based reimbursement contracts of their own. Further, the inclusion of approximately 2% prompt-pay discounts to distributors in the ASP calculation, in addition to the inexorable inflation in drug prices combined with a 6-month lag in ASP updates, meant that the margin on Medicare was never really 6%. In 2012, the application of the budget sequester to Medicare reimbursement decreased reimbursement to ASP plus 4.3%. The cumulative effect on the average oncologist's drug margin is such that it is less than 2.3%.[27]

As margins decreased, the risks inherent to the buy-and-bill system increased. Underwater drugs became common. On the surface, expensive drugs may appear more attractive than a cheaper alternative, but when a drug costs $5,000 and margins are ASP plus 6% minus 2% (prompt-pay discount), minus 1.7% (sequestration), minus 1.3% (price increase), the reimbursement equals 2% or $100. If a patient fails to inform the practice of a new Medicare Advantage Plan with a 20% or $1,000 copay that they cannot pay, the risks are too high. Increasingly, small practices, and even larger ones, report sending some therapies—and more often certain patients, such as those with Medicaid, Medicare with no supplement, and Medicare Advantage Plans with copays on Part B drugs—to

hospitals for infusion.[28] Brown bagging, the practice of having patients acquire chemotherapy through their pharmacy benefit and bringing it to the clinic to have it infused, or white bagging, the outsourcing of chemotherapy to a specialty pharmacy that delivers it to the practice for infusion, has become increasingly attractive for small practices, some of whom have had difficulty obtaining credit.[29]

Larger practices, particularly those in mid-size metropolitan communities with a large community presence, have survived and may continue to thrive in this environment. They have greater buying power and may be able to buy drugs at less than ASP, though the average in ASP requires that their largess be to the detriment of the smaller practice who will find that they then buy at more than ASP. The mega-practice may also have an upper hand in negotiations with commercial payers and benefit from diversification of revenues, capturing downstream revenues such as imaging and pharmacy.[30] Likewise, hospitals with 340B discounts, facility fees, inpatient and outpatient downstream revenue, and commercial contracting leverage do not feel the same pain wrought by the decreasing margins in buy-and-bill chemotherapy.[31]

Given the history, it should be no surprise that the oncologist's sentiment is shaped by personal circumstances. Stereotypical as it may be, it appears that there are four popular responses to the notion of reforming the way we pay for chemotherapy: (1) discouraged and resigned, (2) embittered and angry, (3) removed and aloof, and (4) engaged and innovative.

Discouraged and resigned oncologists have seen and are dismayed by an inexorable increase in the price of oncolytics. The only response they see from policy makers and payers is to decrease the margins available to physicians. They take note that every White House budget proposes paying a lower margin on ASP and they fully anticipate that there will eventually be no margin. Many of them practice in small groups of less than five medical oncologists. They already shift as much risk as possible to hospitals, are acutely aware that they cannot administer the drugs that are underwater this month, brown bag when necessary and are arranging for white bagging, and have a tenuous, at best, line of credit with their distributors. They have or plan to cut staff to bare bones and are actively exploring retirement or negotiating a new employment arrangement. They are too busy generating Evaluation and Management Services to participate in ASCO or state societies. They just wish buy and bill would go away.

To be embittered and angry, physicians have to have practiced long enough to remember buy and bill the way it used to be. Many of the most successful and largest private practices are populated by the embittered and angry. Proud of their independence and the good care that they give their patients, community oncology is a way of life to be defended and fought for. To criticize buy and bill is to criticize their culture, and they feel that ASCO has failed to adequately defend and fight for it. As hospitals grow through acquisition of independent oncologists, they feel further threatened by the relative wealth afforded by facility fees and 340B and angrily seek to level the playing field.

Removed and aloof could be used to characterize many of our young oncologists, indifferent because they do not know better and are content with avoiding the fray through employment. These terms could also be used to describe some oncologists who have left independent practices for the refuge of hospitals, but these should be lumped in with the discouraged and resigned; instead, think of the oncologist who has always been employed and has felt above the fray because of it. They can be found among new hospital partners and in academic institutions. They are proud that their salaries are not tied to how much chemotherapy they prescribe or how expensive the drugs they use are, and they are convinced that their private practice brothers and sisters have succumbed to practice by the margins. They seem oblivious to the fact that the administrators who negotiate their institutional contracts are very much aware of the margins on the drugs they order, or that, should the profit center they work in become a cost center, it may well turn their well-ordered world upside down.

Many oncologists are engaged and innovative. They are growing medical oncology homes, communicating with their local accountable care organizations, engaging with payers to explore payment reform pilots, and building relationships with their representatives in Congress. Many have recovered from discouragement and resignation or evolved beyond bitter and angry, and the lines between community and institution have been blurred. Work is being done by the Clinical Practice Committee's Payment Reform Workgroup to explore alternatives to ASP-based reimbursement to include bundled payments, least costly alternative, shifting Medicare Part B drugs into Medicare Part D, invoice pricing with oncolytics management fees, government/payer negotiation of drug prices, value-based payment, and revamping the Competitive Acquisition Program.

Disclosures of Potential Conflicts of Interest

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CARE DELIVERY AND PRACTICE MANAGEMENT

Beyond the Concept: The Patient-Centered Medical Home in Oncology

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The Patient-Centered Medical Home in Oncology: From Concept to Reality

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OVERVIEW

In recent years, the cost of providing quality cancer care has been subject to an epic escalation causing concerns on the verge of a health care crisis. Innovative patient-management models in oncology based on patient-centered medical home (PCMH) principles, coupled with alternative payments to traditional fee for service (FFS), such as bundled and episodes payment are now showing evidence of effectiveness. These efforts have the potential to bend the cost curve while also improving quality of care and patient satisfaction. However, going forward with FFS alternatives, there are several performance-based payment options with an array of financial risks and rewards. Most novel payment options convey a greater financial risk and accountability on the provider. Therefore, the oncology medical home (OMH) can be a way to mitigate some financial risks by sharing savings with the payer through better global care of the patient, proactively preventing complications, emergency department (ED) visits, and hospitalizations. However, much of the medical home infrastructure that is required to reduced total costs of cancer care comes as an added expense to the provider. As best-of-practice quality standards are being elucidated and refined, we are now at a juncture where payers, providers, policymakers, and other stakeholders should work in concert to expand and implement the OMH framework into the variety of oncology practice environments to better equip them to assimilate into the new payment reform configurations of the future.

Under our current health care system, the care and management of patients with cancer comes with exponentially increasing costs along with compromises in quality of care. Today there are several payment reform models that are being designed and piloted intended to address the desire for evidence-based, value-driven cancer care. One element of this is the OMH concept, which is rooted in the National Commission on Quality Assurance (NCQA) standards originally created for primary care and expanded into specialty medicine. In 2010, Sprandio established an oncology patient–centered medical home (OPCMH) model that showed the ability to control cancer care costs by improving overall management of patients with cancer throughout their treatment.[1] Consultants in Medical Oncology and Hematology (CMOH) became the first oncology practice to be recognized by the NCQA as a level III PCMH, with their OPCMH model. Through NCQA standards, CMOH implemented efforts and aspects of care to target costs, quality, and patient care processes. Results showed that ED visits decreased by 68%, hospital admissions per patient treated with chemotherapy per year decreased by 51%, and the length of stay for admitted patients decreased by 21%. CMOH has shown substantial overall cost savings estimated at $1 million per physician annually. The OPCMH emphasizes the importance of delivery reform in oncology.[2] However, the improved total

costs initially resulted in detrimental financial effect on CMOH. This is partly because the predominant FFS payment system is inadequate to compensate a practice that has implemented the added ancillary services beyond physician-patient interaction and procedures. To comprehensively treat patients with cancer with a well-orchestrated clinical oncology team that enhances care coordination and quality improvements, supporting payment reforms beyond FFS are necessary for the an OPCMH to be sustainable.

To show that community oncology practices can refine patient management processes in a way that manages the care of patients in a cost-effective manner that also improves outcomes with better patient satisfaction, a Centers for Medicare & Medicaid Services (CMS) Innovation Grant of $19.8 million was awarded to Barbara McAneny, MD, through Innovative Oncology Business Solutions (IOBS).[3] Known as the COME HOME Program involving seven community oncology practices in the United States, patients on Medicare are managed under an OMH structure, which includes centralized, protocol-driven triage nurses; extended office hours and 24/7 access to clinical staff; treatment pathways development and compliance; and laboratory/molecular diagnostics efficiency. The purpose of the grant was to show that community oncology practices can become a medical home for patients with cancer, manage the care of these patients in a

cost-effective manner that produces improved outcomes, and provide better patient satisfaction and cost savings. The cost savings were anticipated to come from decreased utilization of more expensive sites of care, such as the ED and inpatient hospital facilities. A small amount of cost savings were to come from the utilization of pathways to standardize triage, diagnosis, and treatment of patients with cancer. This 3-year project is at maturity and preliminary data has shown advantages to the OMH structure as carried out in the COME HOME grant.

Alternatives to the standard FFS and buy and bill practices in the United States have been explored. Gordon Kuntz published first year results of a multipractice, community OPCMH demonstration project in Michigan.[4] The project reduced costs associated with unnecessary ED visits and inpatient hospitalizations. The study suggested that community oncology practices will embrace the transformation to a patient-centered model with properly aligned incentives and administrative assistance.

Newcomer et al of UnitedHealthcare compared five community oncology practices with a large national payer registry of FFS patients and proved that through a gain sharing, episodes of care chemotherapy management coupled with sharing of best-of-practice quality benchmarks resulted in a 34% savings in the community practices compared with matched controls under FFS.[5] The University of Texas MD Anderson Cancer Center has contracted with UnitedHealthcare to manage all aspects of head and neck cancer care from diagnosis to death under a true yearly bundled payment system. This payment method conveys a much higher risk to the provider, but with the potential for greater financial rewards for optimal patient management. The inherent risk of this payment model may be acceptable by large institutions but adverse for most independent practices.

Recently, CMS has clearly announced their intent to accelerate payment structures that move away from FFS and into accountable, value-based bundled payments.[6] For oncology practices to remain viable going forward, successful management of the financial risks that are intrinsic to bundled payments can be lessened by incorporating OMH processes. These are directed at maximizing global patient management according to appropriate accredited benchmarks.

REWARDING PERFORMANCE IN MEDICAL ONCOLOGY

A basic economic principle states that higher risk should have the potential for higher rewards. Building an OMH requires additional time and resources and this investment does not make sense unless there is potential return for the extra effort. This section discusses the new funding mechanisms being employed to compensate for better medical oncology performance. Potential, however, is not a guarantee of reward. Installing the processes is not enough. The outcomes must be better than standard performance to earn higher rewards.

There are several options being used for performance-based compensation (Fig. 1). The lowest risk form is pay for performance. In this model, a bonus is paid for attaining predetermined targets. Typically these targets are process measures rather than outcomes. These process measures are expected to produce better outcomes, but time and data limitations often prevent the actual outcomes measurement. Generally, the payments are small and the measures can be obtained using claims data. The pay-for-performance model has been popular for providers with large populations like primary care practices or accountable care organizations. The model does not work as well for medical oncology because of the small patient numbers and the relatively small payments for an individual practice.

Anthem uses an interesting variation of the pay-for-performance model that pays a management fee for treating patients with predefined chemotherapy regimens.[7] No measurement is required because the payment begins immediately for each compliant patient. The payment is also larger than most pay-for-performance programs (approximately

KEY POINTS

- As we look at fee-for-service (FFS) alternatives, several performance-based payment options exist with ranges of financial risk, reward, and accountability.
- Oncology medical homes (OMHs) have been shown to improve patient care, patient outcomes (less emergency department and hospital admissions), patient satisfaction, and with substantial cost savings to the payers.
- The OMH practice infrastructure required to create cost savings is not covered under traditional FFS. Rewards for OMH performance should be based on a small number of meaningful quality performance measures.
- To cover practice costs of an OMH, practices will need to enter payer contracts that recognize the value of all services provided.
- An OMH infrastructure gives the best opportunity for sustaining contracted bundled payments with risk sharing/shared savings, which are anticipated in the near future.

FIGURE 1. Reinforcing Engagement of the Physician: Value-Based Provider Contracting
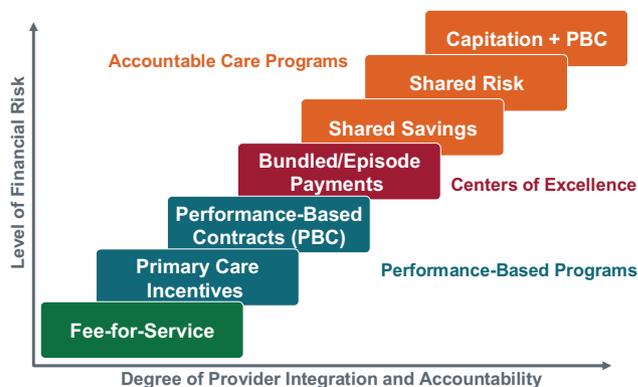
$350 per month per patient). The regimens were selected by an expert physician panel based on outcomes from the medical literature. Anthem expects the lower total cost of the selected regimens to fund the program payments. There is no penalty for using other regimens.

Risk sharing or gain sharing is the next progression of payment risk. Physicians in these programs have their managed patient's outcomes measured and compared with another similar population. Any savings in the managed group is shared between the payer and the clinicians. Gain sharing is participation only in savings, whereas, risk sharing often implies that the physician would share in losses as well. The key to an accurate program assessment is the quality of the comparison group. Many risk-sharing contracts utilize a year over the previous year comparison within the same practice. This method often cannot adjust for the change in patient diagnosis mix resulting in an inaccurate assessment of savings. The ideal comparison group is treated during similar timeframes and can be risk adjusted to match those patients in the managed practice. The approach is no different than a well-conducted clinical trial.

The next progression of risk is the bundled payment, which is the ambulatory equivalent of the Diagnosis Related Group (DRG) used for hospital reimbursement. A fixed payment is made to the provider for the services required to care for a specific diagnosis. These payments often include multiple disciplines and facilities. The recent MD Anderson Cancer Center contract with UnitedHealthcare illustrates the components of a bundled payment. Patients with head and neck cancer are evaluated at the cancer center and assigned to one of four risk categories. All of the services required for the complete treatment of this patient are included under a single payment from the payer. The bundle covers a 1-year time period including complications. Bundles provide the incentive to remove all of the unnecessary or nonvalue services to maximize profit. The MD Anderson Cancer Center used a systematic approach to map the processes for head and neck cancer treatment and activity-based accounting to identify and remove unessential care. Similar to the DRG, the elimination of complications is the other substantial way to improve profits under this payment system. Quality pays in bundled payments.

Capitation is the highest form of risk. The capitated provider assumes complete financial responsibility for all cancer care in a population of patients within a fixed budget. The population must be well defined with risk profiling, and actuarial expertise is essential to manage this type of payment. Very few organizations are capable of undertaking this type of contracting and the authors discourage providers from attempting this approach until they have mastered other lower-risk programs.

IMPORTANCE OF ESTABLISHING PERFORMANCE MEASURES

Medical practices who assume risk need infrastructure to understand the processes they use to evaluate and treat their patients. Mapping those processes will be both enlightening and startling because inconsistency is usually the norm. Adopting and driving standard approaches to common problems eliminates waste and increases productivity—changes that make risk contracting a profitable approach. At the same time, the new understanding of patient care performance drives higher quality with fewer errors, better communication, and rapid identification of patient problems.

Those new changes are managed with internal performance measures. No practice should assume things are changing because they signed a risk contract; the change must be measured and managed. These internal, quality improvement measures can be less rigorous than external measures and they can be adjusted frequently. The purpose of these measures is not to obtain complete accuracy, but rather to identify trends quickly and make adjustments. Adopting this type of measure is difficult for physicians who are used to exact measures of performance.

External measures are more rigorous and are often tied to compensation. These measures should be limited to the vital few because the data collection and analysis are time consuming. Regulators often require multiple measures as an assurance of quality in risk programs, but if too many measures are required it can discourage participation by physicians. Further, risk payment should not be hindered by measures that are not required of FFS providers. The best external measures are quite simple: survival, either disease-free or overall, and total cost of care. Adding process measures that contribute to these two ultimate measures distract physician resources during the risk contract.

These principles have moved beyond the theoretical. A recent pilot for a gain-sharing episode payment demonstrated a 34% savings in the trial cohort compared to matched controls in FFS payment models.[5] The MD Anderson Cancer Center has initiated a full bundled payment for patients with head and neck cancer. Models like these have the potential to drive higher quality care while simultaneously saving money by eliminating unnecessary care.

COME HOME OUTCOMES AND SUSTAINABILITY

OMHs have been shown by the COME HOME Program to meet the triple aim: Patient care is improved, and patient outcomes are better (lower ED visit rate, lower inpatient admission rate, fewer inpatient days) with consistently high patient satisfaction, all at an equal or often lower cost than local comparator groups.

Participating oncology practices provide all outpatient cancer care, including triage pathways that ensure patients receive the right care in the right place at the right time for symptoms related to cancer and cancer treatment (Fig. 2), and clinical pathways that address appropriate imaging, pathologic testing, and molecular diagnostics, and delineate chemotherapy, radiation oncology, supportive care, and surgery (when applicable). The best practices offered by OMHs include patient education and medication management counseling, team-based care, 24/7 practice access (telephone

FIGURE 2. Triage System Utilization by (A) Outcome and (B) Time of Triage Call
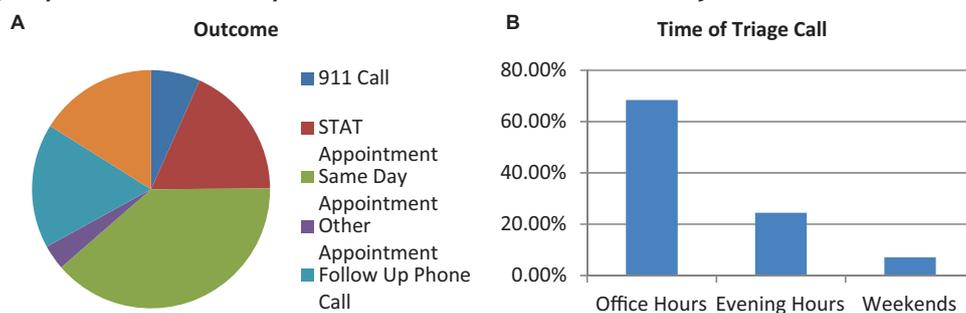
triage, evening/weekend clinic hours, electronic health record [EHR] access through patient portals and on-call clinicians), on-site or near-site imaging and laboratory testing, and admitting physicians who shepherd patients through inpatient encounters, avoiding handoffs and readmissions, to ensure seamless, safe, and efficient care. Further, the COME HOME program offers physicians and administrators from community oncology practices unprecedented access to real-time quality, pathway adherence, and utilization data, including provider-level measures and benchmarking within each practice and within the COME HOME Program.

The medical home infrastructure creates four sets of costs that are not covered under traditional FFS and must be addressed using an alternative payment model.

1. Medical homes need triage nurses, patient care coordinators, data analysts, lab technicians, and other staff to meet the goal of providing the right care at the right time in the right place. However, most of the services provided by these staff are not billable under a FFS contract.

2. The medical home relies on leaving daytime physician time available, thus, running the risk that a valuable commodity (physician time) will go unused and, therefore, generate no revenue (opportunity cost).

3. Treating patients with the hydration and symptom control treatments instead of using the infusion center overhead for chemotherapy replaces better paying services with services given at a loss.

4. Offering evening and weekend clinic hours for the infusion of antibiotics, symptom control medications, and hydration will keep patients out of the ED and hospital, but does not generate sufficient evaluation and management and infusion codes to cover the salaries of personnel. During these after-hours clinics, at least two nurses and associated support staff must be present, but the services provided, such as hydration and intravenous antibiotics administration, generate very low reimbursements.

Under the medical home infrastructure as described above, participating practice sites have shown a 23% to 28% reduction in the percent of patients with ED visits (Figs. 3 and 4). Treating patients in a physician's office after hours rather than sending them to the ED saves payers money, but it actually costs physicians more money to provide the care than they are reimbursed. To cover practice costs of a medical home, the COME HOME program practices will need to enter into contracts with payers that recognize the value of the services provided. These services generate savings through reduced ED and inpatient use, but these savings only accrue to the payer. We see bundled payments, with options for risk sharing/shared savings as the best contracting option for sustaining the medical home infrastructure.

Oncology bundled payments and other risk-sharing arrangements are highly innovative, untested, and financially risky to physician practices. COME HOME is now beginning to develop the necessary knowledge base to support bundled payments/shared savings in this arena. Together with the COME HOME practices, the team at IOBS has launched two related efforts to support future oncology bundled payments with shared savings. First, they are developing a data analytics infrastructure that will allow for the participating practices to track improved outcomes, understand their costs for treating common cancer types (breast, lung, and colon) and be familiar with sources of savings from the medical home model to set bundled price targets/shared savings in a transparent and data-driven way. Second, IOBS is conducting a series of limited bundled payment pilots with small patient pools. These pilots allow the participating practices to become familiar with bundled payment mechanisms while limiting overall risk. Both of these activities are ongoing at the moment, and they often inform each other.

FIGURE 3. The COME HOME Beta Site Percent of Patients with Emergency Department Visits
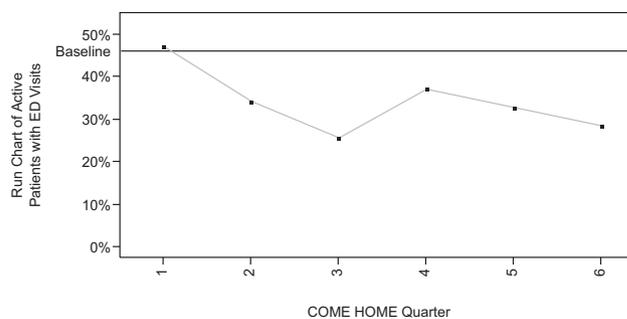
The COME HOME beta site shows a 23% reduction in the percent of patients with emergency department visits.

FIGURE 4. The COME HOME Beta Site Percent of Patients with Emergency Department Visits
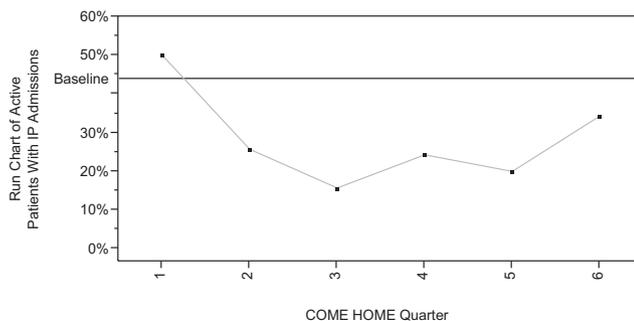
The COME HOME beta site shows a 28% reduction in the percent of patients with emergency department visits.

BEYOND THE CONCEPT: THE ONCOLOGY PATIENT-CENTERED MEDICAL HOME

OPCMHs, like other emerging models of cancer care, delivers value by improving quality through standardized processes, minimizing the variation of care, and lowering cost by reducing the overutilization of services associated with the variable delivery of care. Oncology Management Services (OMS) served the CMOH, as it became the first medical oncology practice to be recognized by the NCQA as a level III PCMH in 2010. Since then, CMOH has continued to demonstrate reduction in unnecessary utilization, while driving the consistency and quality of care. The practice reports an ongoing, cumulative reduction in ED utilization rates of 78% and reduction in hospitalization rates of 50% per patient on chemotherapy per year (2007 to 2013). This progressive improvement is attributed to ongoing standardization of process, workflow, data collection, data presentation, documentation of response to data, and communication, along with improved patient engagement and enhanced access. CMOH's current rates of ED utilization and hospital admission remain substantially below the market as confirmed by collaborating regional payers.

Currently, 48% of CMOH's patient base is covered with OPCMH-related contracts that align payment with the demonstration of results. CMOH has sustained a staff:physician full-time equivalent ratio of 5.6 since 2011 (previously 8.3 in 2008). Furthermore, as a result of progressive enhancement of patient engagement and education, there has been a change in patient behavior to the point where CMOH no longer provides extended hours of operation. The majority of symptom-related calls within their patient population occur during normal hours of operation.

OMS provides consultation services and supports the transformation of community- and hospital-based oncology practices by leveraging the current NCQA Patient-Centered Specialty Practice (PCSP) recognition standards, as well as a comprehensive and proprietary set of transformation tools, optionally supported by internal practice-related performance analytics and information technology.

Practice and program transformation to this or similar models enables a new value proposition and participation in emerging alternate payment methodologies for cancer care that are now being promoted by commercial payers, as well as Medicaid and Medicare, including the recently designed CMS Oncology Care Model (OCM).

VALUE IN CANCER CARE

Health care reform is focused on value and the demonstration of results. Value is commonly defined as some variation of the equation quality/cost. Let's review the Institute of Medicine's (IOM) definition of quality in health care as it relates to cancer care (Fig. 5).

- Quality is: "The degree to which health services [center column on diagram] delivered to individuals or populations increase the likelihood of desired health outcomes [left column] and are consistent with current professional knowledge [right column]."
- Value can be defined using the IOM definition of quality care delivered with the proper allocation of resources (cost).

It has become recognized by patients and payers that the utilization of unnecessary resources— often, a result of the execution of even the most artfully constructed treatment plan—is poor quality care, no matter the degree of adherence to the evidence base. Transformation of a practice to a PCMH-related model is related to improving the consistency of the activities of a coordinated care team.

The effectiveness and efficiency of the physician-led care team's activities (primary driver, center column) drive the desired payer- and patient-centric outcomes (left column). In cancer care, the desired outcomes are self-evident: guideline-based multidisciplinary care, improved patient experience, prompt palliation of symptoms, reduction in unnecessary resources, coordinated survivorship care, rational care at the end of life, and control of cost by focusing on the reduction of unnecessary resource utilization.

There are well-recognized quality performance metrics in the domain of secondary drivers, the evidence base (right column). Oncology is rich in externally recommended treatment standards from which all cancer care providers benefit: National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and Commission on Cancer (COC) all have created guidelines. In the OPCMH model, validated process standards (NCQA, American College of Physicians, National Coalition of Cancer Survivors) are equally important secondary drivers of quality, cost, service, and practice efficiency.

Value and quality metrics are embedded within all three columns of the driver diagram (Fig. 5). As we study and understand which specific process-related activities drive outcomes, we can better define future quality measures (i.e., turnaround time, content and dissemination of documentation). Quality measures (based on the IOM definition) will not be limited to well-recognized evidence-based standards or even outcomes; rather, the emergence of practice-level performance-based metrics that are proven to drive desired outcomes.

FIGURE 5. Oncology PCMH Quality and Value Driver Diagram
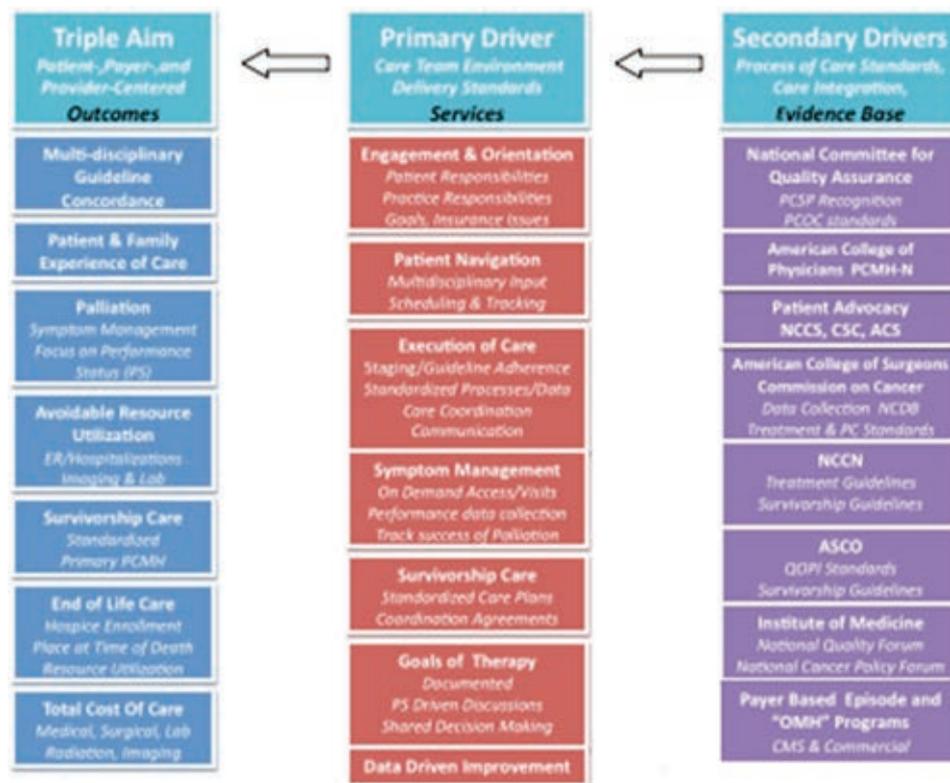
The real focus of oncology practice transformation is how efficiently the physician-led care team—the primary driver of quality and cost—actually delivers care while adhering to the secondary drivers of the evidence base and validated process standards.

PAYER SUPPORT

The last of the seven *Joint Principles of PCMH,* a collaborative effort to standardize the PCMH model for primary care, calls for "appropriate payment recognizing the added value of the model."[8] Payer recognition of the variability of cost and quality, and the willingness to align appropriately motivated changes in care delivery was critical to the adoption of the model by primary care providers. The same holds true for specialty care providers, most notably oncology. As outlined in the OPCMH payer-provider collaboration diagram (Fig. 6), several synergistic activities and commitments between providers (right column) and payers (left column) drive performance enhancement within the care team (center column).

By focusing on the essential demand for improved quality and value regardless of the payment model or organizational structure of the parties adopting it, transformed practices can become providers of choice by driving consistency of the execution of care and being flexible enough to accommodate whatever payment changes may come in the future:

performance-based, budgeted (episodic or bundled), or progressive risk-assuming contractual models.

PROCESS AND POLICY STANDARDS

The NCQA has played a dominant role in defining standardized and validated processes of care delivery that provide direction for infrastructure development, enabling practices to focus intently on the way that primary care is delivered. Many of these standards are applicable to both primary and specialty care as they relate to patient access and communication, the identification and coordination of patient populations, the planning and management of care, the tracking and coordination of care, and measurement and improvement of practice performance.

In March 2013, the NCQA released the PCSP standards that are applicable to all specialty practices, especially those involved in longitudinal care of medically complex patients. Current NCQA PCSP standards serve as the foundation for transformation of the cancer care team activities. These activities include patient engagement and orientation, patient navigation, execution of care, symptom management, survivorship care, goals of therapy and end-of-life care.

Furthermore, the NCQA, in conjunction with ASCO, the RAND Corporation, OMS, National Coalition for Cancer Survivorship, and Independence Blue Cross, is refining oncology-specific patient-centered oncology care (PCOC)

FIGURE 6. Oncology PCMH Payer/Provider Collaboration
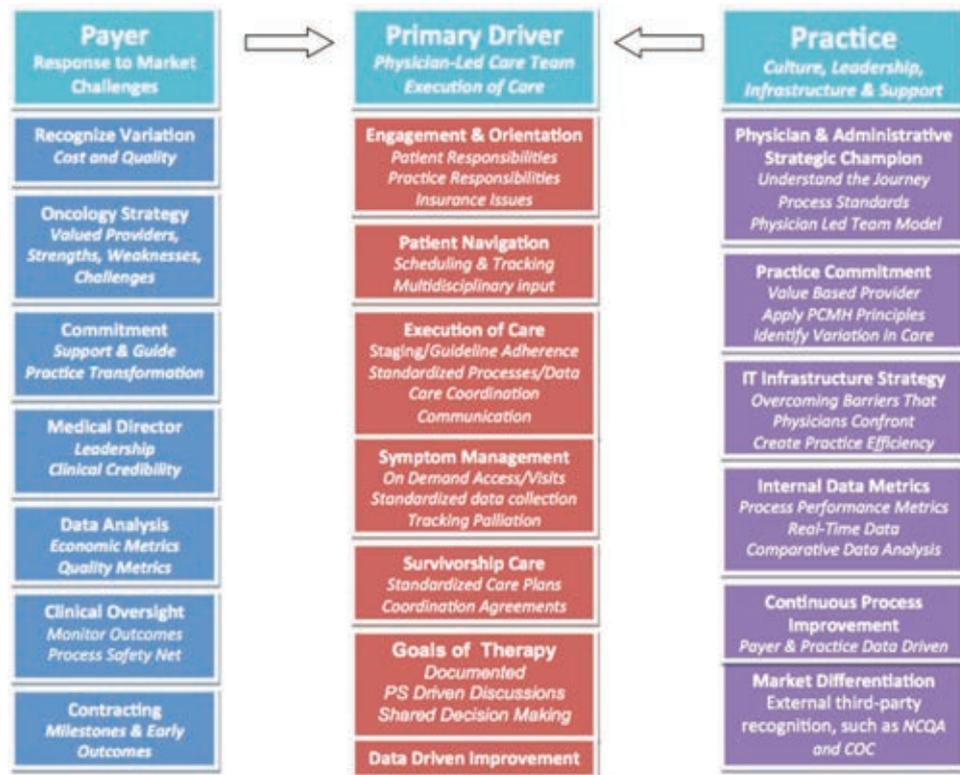
standards within a Patient-Centered Outcomes Research Institute–funded project in southeastern Pennsylvania. This project is studying practice transformation in five practices in community- and institutional-based settings. Process standardization is encouraged, with each practice having the freedom to develop specific processes most appropriate to their individual sites. The use and optimization of technology is encouraged, but not mandated, as one of the participating practices does not even use an EHR. It is anticipated that the NCQA PCOC standards will be finalized during the course of the project. The PCSP and PCOC standards are complementary to the CMS OCM, reinforcing the common processes and service components required for the creation and demonstration of value by the oncology care team.

It is anticipated that additional nongovernmental organizations will be providing certification or recognition of cancer programs and practices including ASCO, the COC, and The Joint Commission.

IS A PATIENT-CENTERED MEDICAL HOME IN ONCOLOGY SCALABLE?

Scalability is important to both payers and providers. Practices recognize that innovative care models provide them with a new value proposition and the option of participation in emerging payment methodologies. Broad scalability among practices requires a model that guides process standardization that is effective yet flexible to best suite each prac-

tice's existing environment and infrastructure. The goal is to streamline and standardize existing processes, not the disruption of effective services and workflow. Practice affordability is another issue; willingness to transform will, in part, depend on practices understanding the importance of process standardization, not only as a driver of value, but with optimal information technology support, as a major driver of practice and provider efficiency (refer to the section on CMOH results).

Payers desire uniformity of the outcome goals and cost control as well as broad adoptability throughout their provider networks. Payers also desire flexibility regarding the payment methodology. OMS is involved in several payer-provider transformation projects. There is common ground regarding the goals of every oncology-related payer-provider experiment underway— enhance quality and control cost. However, each of the projects involves innovative payment methods that vary considerably and are based primarily on the uniqueness of markets, sometimes the patient population, and in large measure, payer- and practice-related data reporting capabilities.

Scalability will require one more important step. During the last 90 years, a number of professional organizations and patient advocacy groups have provided invaluable leadership and direction regarding quality and service standards to the cancer care community. Many of these organizations, along with a growing number of payers, understand the importance of adopting specific PCMH-related standards to cancer

care and the value created. These important organizations could continue to provide leadership by collaborating to develop a core set of cancer care standards, elements, and features to enhance the focus, minimize the confusion, and shorten the timeline for adoption of new cancer care models within the payer and provider communities. Unification and working toward common patient and provider goals will enhance adoptability, and, therefore, scalability.

CONCLUDING REMARKS

Innovative payment models in cancer care are getting increased attention from all oncology stakeholders, including CMS, private payers, providers, drug manufacturers and distributors, hospitals, professional societies, and, importantly, the patients. Faced with spiraling costs, regulatory burdens, impaired access to treatment, and inefficiencies of care there has been a driven focus on delivering cancer care with greater value to all the stakeholders. The OPCMH concept has now been shown to be a viable foundation for carrying out quality-driven, cost-effective comprehensive management of patients with cancer. Much of the value gained from the OMH infrastructures comes through refinement of day-to-day patient care processes resulting in superior outcomes.

Practices should be held accountable to quality practice standards through established and developing accreditation standards through entities such as NCQA and COC, as well as adherence to recognized treatment guidelines and pathways. The further development of these quality metrics should be evidence-based, succinct (clinically relevant), advocate the patients' best interests, and with expert consensus from all stakeholders.

As it becomes acutely apparent that a major element of health care reform is to move away from FFS to varieties of bundled payment options, we believe that the PCMH models in oncology can provide the stable infrastructure required to mitigate the inherent financial risks of bundled payment, episodes of care, and share savings payment options. However, without payer support, further attrition of community-based practices can be anticipated, resulting in escalating costs and a decline in the value of cancer care. It is important for payers and policymakers to understand that for providers to implement substantive practice management changes that provide higher quality care at lower costs under a system other than FFS, it is mandatory that the financial value of uncompensated comprehensive services provided through an OMH program be recognized to be sustainable and scalable.

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CARE DELIVERY AND PRACTICE MANAGEMENT

ICD-10: History, Implementation, and Opportunities

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A Strategic Plan for Integrating ICD-10 in Your Practice and Workflow

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OVERVIEW

The adoption of the International Classification of Disease (ICD) 10th Revision (ICD-10) diagnosis code set in the United States has been legislatively delayed several times with the most recent date for implementation set for October 1, 2015. The transition from ICD-9 to ICD-10 will be a major undertaking that will require a substantial amount of planning. In the following article, we outline the steps to develop and implement a strategic plan for the transition to the new code set, identify training needs throughout the practice, and review the challenges and opportunities associated with the transition to ICD-10.

Unless there is another delay, the United States will transition from ICD-9 to ICD-10 in all health care settings on October 1, 2015. This will not be a gradual transition as there will be no grace period. Still, the replacement of ICD-9 with ICD-10 as the Health Insurance Portability and Accountability Act (HIPAA)-named code set did not come without plenty of notice. Before we get into the practical elements of ICD-10 implementation and the opportunities associated with the implementation of ICD-10, let us step back and take a brief look at the history of the ICD.

The first international classification edition was adopted in 1893 by the International Statistical Institute and was called the International List of Causes of Death. The ICD has been revised over the years and is now the standard diagnostic tool for epidemiology, health management, and clinical purposes. It is used globally as the foundation for the identification of health trends and statistics.[1]

The World Health Organization (WHO) has been maintaining and publishing the ICD since 1948, with periodic revisions. To date, there have been 10 revisions of the ICD; the most current edition is ICD-10. The United States has used ICD to classify the causes of death since 1900 and is currently using ICD-10 to report causes of death.

In 1979, the WHO adopted ICD-9, and, with the approval of WHO, the United States adopted a modified version of ICD-9, the International Classification of Diseases Clinical Modification (ICD-9-CM), to assign codes to diagnoses associated with inpatient, outpatient, and physician office utilization, and the International Classification of Diseases Procedure Coding System (ICD-9-PCS) to assign codes associated with inpatient procedures.[2]

WHO adopted ICD-10 in 1994, and, once again, the United States received approval from WHO, which owns and publishes the classification, to develop a revised ICD-10-CM for use in this country. However, although the developed ICD-10-CM codes are updated annually, we have yet to adopt them.

The U.S. Department of Health and Human Services first published a proposed rule to replace ICD-9-CM with ICD-10-CM in August 2008. At that time, it proposed an effective date of October 1, 2011, for the transition to ICD-10. Since then, the ICD-10 deadline has been postponed three times (Fig. 1).

The American Medical Association (AMA) has been very vocal in their opposition to the adoption of ICD-10. Still, in a letter to the Centers for Medicare & Medicaid Services (CMS) just before the most recent delay, the AMA acknowledged that there were other "well-intended" stakeholders in the health care industry that are advocating the move to ICD-10. In their letter, the AMA asked CMS to implement the following provisions if they were intent on adopting ICD-10:

1. A 2-year implementation period during which Medicare will not deny payment based on the specificity of the ICD-10 code, will provide feedback to the physician on any coding concerns, and will not recoup payment because of a lack of ICD-10 specificity.

2. When the most specific ICD-10 code is submitted no additional information will be required to adjudicate the claim, particularly in the absence of an attachment standard.

3. Physicians would be eligible for advance payments when the physician has submitted claims but is having problems getting the claim to reach the contractor because of problems on the contractor's end; a physician

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FIGURE 1. ICD-10 Legislative Timeline

Overview of ICD-10 Legislation

➤ **August 15, 2008** - Department of Health and Human Services (HHS) publishes proposed rule to replace ICD-9-CM with ICD-10-CM effective October 1, 2011.
➤ **January 2009** - HHS publishes the final rule for adoption of ICD-10-CM and ICD-10-PCS, setting a compliance date of October 1, 2013 (rather than the proposed date of October 1, 2011).
➤ **April 2012** - HHS releases a proposed rule calling for a 1-year delay for the ICD-10 compliance date from October 1, 2013 to October 1, 2014.
➤ **April 1, 2014** - President Obama signs the bill, Protecting *Access to Medicare Act of 2014* into law, which mandates that ICD-10 cannot be implemented before October 1, 2015.
➤ **May 1, 2014** - CMS announces new compliance date of October 1, 2015 and states that HIPAA covered entities are required to continue to use ICD-9 through September 30, 2015.

ICD-10-CM

(Clinical Modification)

The <u>diagnosis</u> code set that will replace ICD-9-CM Volumes 1 & 2:

- Will be used by all providers in every health care setting
- CPT/HCPCS will still be used for outpatient and physician office procedures

ICD-10-PCS

(Procedural Coding System)

The code set of hospital inpatient <u>procedures</u> that will replace ICD-9-CM Volume 3

Abbreviations: ICD, International Classification of Disease; CMS, Centers for Medicare & Medicaid Services; CM, clinical modification; CPT/HCPCS, Current Procedural Terminology/Healthcare Common Procedure Coding System; PCS, procedural coding system.

has not been paid for at least 90 days; at least 25% of their patients are on Medicare; or at least 25% of their reimbursements are from Medicare.

The Protecting Access to Medicare Act of 2014, implemented on April 1, 2014, includes a provision that the Secretary of the U.S. Department of Health and Human Services may not adopt ICD-10 before October 1, 2015.[3] Nevertheless, not everyone was in favor of another delay in ICD-10 implementation. The American Hospital Association, most of the national payers, and the American Academy of Professional Coders lobbied against another delay.

Absent another delay, effective October 1, 2015, ICD-10-CM will replace ICD-9 as a HIPAA-named code set to be used on electronic, paper, fax, and phone transactions by HIPAA-covered entities, which include providers, payers, health care clearinghouses, software vendors, and third-party billing services. Furthermore, ICD-9-CM will not be maintained after implementation of ICD-10-CM, thus non-covered entities will also likely transition to ICD-10.

CREATING AND MAINTAINING A HOLISTIC ICD-10 READINESS PROGRAM

No matter if a practice is a five-physician oncology clinic or a 100-plus multispecialty physician group, a holistic approach to ICD-10 preparation is essential. For example, if a health system is focused primarily on application readiness, then issues would occur with lack of staff knowledge, workflow, gaps in clinical documentation, mitigation of payer risk, and care team overall readiness.

Below are examples of work streams that would be part of a holistic remediation approach we will describe in the following sections:

- Communication and engagement
- Application remediation and testing

KEY POINTS

- The International Classification of Disease (ICD) is used globally to identify health trends and statistics.
- In 1994, the World Health Organization adopted the 10th revision of the ICD, ICD-10.
- Despite the advantage of more precise coding under ICD-10, the United States has delayed adoption of the code set several times.
- The transition from the current ICD-9 code set to ICD-10 is a major undertaking that will require significant resources.
- Careful systematic planning is necessary to minimize costly disruptions and errors during the transition.

SIDEBAR. ICD-10-CM versus ICD-10-PCS

ICD-10-CM (Clinical Modification)
- The diagnosis code set that will replace ICD-9-CM volumes 1 and 2 and will be used by all providers in every health care setting
- Current Procedural Terminology/Healthcare Common Procedure Coding System (CPT/HCPCS) will still be used for outpatient and physician office procedures

ICD-10-PCS (Procedural Coding System)
- The code set of hospital inpatient procedures that will replace ICD-9-CM volume 3.

- Training and clinical documentation improvement
- Payer engagement and readiness
- Denial management
- Data warehouse and reporting

Along with having a balanced approach to remediation, it is important to have the right people involved, especially since ICD-10 conversion will affect essentially every role in an organization. Every person in the practice needs to know how ICD-10 will affect their daily routines. Establishing an overall ICD-10 leader and leads for each of the work streams above is ideal, and for many leads this responsibility should fall under their current role in the practice as business office manager, coding lead, trainer, etc.

To gain the leadership and financial support needed to be ICD-10 ready, it is important to have a physician champion and involve practice leadership in planning, risk mitigation, and education events to be prepared for the effects of ICD-10. Engage physicians and clinicians to understand how improved documentation will be required as part of being ICD-10 ready. Creating awareness across departments on codependent readiness tasks is needed to ensure that the right people are working together on tasks like workflow readiness, claims edits/rules remediation, reduction of unspecified codes, end-to-end testing, etc.

When practices work together on large transformations like ICD-10, it is a great opportunity for practice staff to collaborate across functional areas and learn how they are all dependent on each other to provide care to patients and maintain a high-performing revenue cycle process. Because of the duration and complexity of migrating to ICD-10, having an integrated project plan, ongoing issue and risk management process, and change management plan have been essential to managing decision making and change over an extended timeline. Much of ICD-10 readiness is risk mitigation for assurance that after October 1, 2015, the effect is minimal and a steady-state can be achieved soon after.

ENGAGEMENT AND ONGOING COMMUNICATION

Awareness throughout a practice on ICD-10 conversion (i.e., why, when, and how) needs to be continuous and widespread. Conversations on ICD-10 need to be part of weekly meetings of all teams, and regular round table meetings with the ICD-10 work-stream leads need to occur to be able to follow through on an integrated plan with strong codependencies. Every practice's culture is different and effective communication methods will vary; always be sure ICD-10 conversion is part of the conversation and every planning session. Team with your physician champion to keep ICD-10 at the forefront of conversations with his or her colleagues.

APPLICATION AWARENESS AND TESTING TO VALIDATE READINESS

Every application that contains and utilizes diagnosis codes in a practice will be affected by ICD-10 and will need to be on an ICD-10–compliant version and tested before conversion. Practices need to target their electronic health record (EHR), practice management system, laboratory information system, radiation oncology information system, claim scrubber, and any other application that carry codes for remediation. Mapping out systems affected, along with interfaces and application version required, is a basic first step to know what will need to be remediated and ready for conversion. Spend the time to keep in regular contact with application vendors to know what is required and has changed as the vendor also prepares for ICD-10.

Preparedness for ICD-10 requires more than just having each application on an ICD-10–compliant version. Applications need to be tested end to end in a nonproduction (i.e., live) environment before activating ICD-10 codes on October 1, 2015. This testing is essential to identify major defects, issues, and workflow that need attention from the point of documentation in the her, to the practice management system through the claim scrubber, and then clearinghouse to the payers and back. Ideally, a practice would have a chance to participate in acknowledgment and end-to-end testing with Medicare by teaming with a Medicare Administrative Contractor (MAC). End-to-end testing MACs and private payers often only target select providers, which limits end-to-end testing opportunities for many practices. Practices need to test early and often to minimize the potential risk of activating ICD-10 code across all applications on October 1, 2015. The Nachimson Advisors Study on ICD-10 readiness estimates ambulatory practices will spend $4,300 to $9,600 per physician on application end-to-end testing efforts and guidance.[9]

TRAINING FOR ALL PERSPECTIVES AND CLINICAL DOCUMENTATION IMPROVEMENT

Because of the diverse effects of ICD-10, training needs to be widespread and encompassing to ensure all practice staff are clear on how ICD-10 will affect their work environment. When determining who needs training, consider targeting all physicians, advanced practice providers, nurses, medical assistants, radiation therapist, coders, all business office staff, front-office staff, and any other staff members that are dependent on diagnosis codes. The Nachimson Advisors Study estimates practices will spend $480 to $1,000 per physician on training of staff and themselves.[9] This cost varies by practice size and type of training and does not include the cost of physicians' and staff's time. The study also estimates a physician will need an hour of documentation training, which will likely be the minimum, and training for coding and other staff will be much more time consuming.

Utilize a mixture of training methods to help meet the different learning needs and challenging schedules of providers and staff. Consider attending boot camps to set aside dedicated time for those who will be affected the most. Providing access to eLearning, podcasts, and illustrations of common diagnoses can help make learning more on demand and accessible. Many coders are looking to become ICD-10

certified to help assist their practices in being ready for the conversion.

Providing coders the opportunity to become ICD-10 certified is a good idea to promote the sharing of knowledge among coders and throughout the practice as a whole. Coders should also be an essential part of establishing a closed-loop process for reducing the use of unspecified codes and increasing the specificity of documentation and coding. Teams need to focus on reducing the use of unspecified codes now to decrease the risk for increased denials with ICD-10 because of lack of documentation specificity. Increased specificity means documenting more details on location, laterality, severity, sequelae, duration, stage, cell type, etc. If documented in a structured manner, some EHRs can use documentation to assist providers in selecting a diagnosis. For example, some EHRs will reduce the list of diagnoses or problem codes to ease selection based on laterality, stage, etc., and also alert the clinician when there is not enough documentation to support a specific code.

Many practices are applying the concept of dual coding to help staff learn by practicing documenting and coding in ICD-10. A dual-coding regimen leading up to the conversion can also help practices prepare for the productivity effects of coding in ICD-10 compared with ICD-9 by measuring side-by-side productivity. Dual coding can also help identify areas for clinical documentation improvement.

PAYER ENGAGEMENT AND MONITORING READINESS

Teaming with payers is essential, but it is also a challenge. Many payers are only testing with select providers or recommending that providers only test with clearinghouses and vendors. Ideally, providers would be able to perform end-to-end testing with all of their high-volume payers and receive a full round-trip test and testing results from the payers. This provides the best representation of the actual process and eventual results of converting to ICD-10 on October 1, 2015. Take advantage of any opportunities to test with Medicare, whether it be acknowledgment or end-to-end testing. For end-to-end testing with Medicare, MACs target select clearinghouses and providers, therefore practices should register to have a chance of being selected.

Payer readiness is uncontrollable from a provider perspective. Project teams should work diligently to gauge the readiness of their high-volume payers. Identify any risk that can potentially be mitigated by asking payers how they plan to handle activation tasks and stabilization support after converting to ICD-10. For example, know when payers have updated their medical policies and how they plan to handle authorization before and after the conversion.

DENIAL MANAGEMENT FOCUS ON METRICS, WORKFLOW, AND PERFORMANCE

Proactive monitoring and elimination of denials is typically part of the daily fabric of a practice's business office. With ICD-10, practices need to actively work today to reduce the potential of new future denials by increasing the specificity of documentation. Care team education and awareness on required documentation and tracking unspecified code utilization to target areas for improvement are two attributes of a closed-loop approach to improve documentation.

Comprehensive and timely metrics are essential for practices to track denial trends leading up to and after the conversion to ICD-10. Tracking performance after conversion will let practices know when steady-state has been achieved or target areas to address to get back to steady-state. Refine denial and rejection metrics to target denial reasons that are driven by diagnoses and coding. This is a good way to target areas for improvement that would otherwise be exacerbated with the introduction of ICD-10.

ICD-10 workflow remediation is the perfect opportunity to look at your denial management workflow from start to finish. Reduction of current and potential future denials can be accomplished through collaboration across teams, targeting areas for improvement based on denial trends, education, and new policies and procedures to invoke and maintain change. This is a good opportunity to apply Lean Six Sigma principles with the team for long-term improvement.

NAVIGATING CHANGE THROUGHOUT ICD-10 CONVERSION

Change is inevitable during long-term programs like ICD-10 remediation and especially now with an extended timeline. Have mitigation plans in place to help prepare for and adjust to change. There are obvious substantial changes, like the delay of ICD-10, but again with the duration of this type of remediation, always prepare for other events such as staff turnover, new substantial projects, application migrations for meaningful use, etc.

Any controllable changes definitely need to be addressed before the 90 days leading up to the ICD-10 conversion date. Ideally, this 90-day period would be a freeze period with no change to prepare for activation of ICD-10.

Beyond the inherent benefits of converting to ICD-10, seize this opportunity to achieve as much long-term value as possible from remediating practice processes, improving performance, and creating a team-based approach to improvement. Always take advantage of large systemic changes like ICD-10 to take a renewed look at how the practice team collectively provides patients access to care.

DETERIORATING QUALITY OF HEALTH CARE DATA

The quality of health care data progressively deteriorates as long as the United States continues to rely on the outdated and imprecise ICD-9-CM code set. By continuing to use the outdated ICD-9-CM code set, the United States has limited ability to extract information that will optimize public health surveillance, exchange meaningful health care data for individual and population health improvement, and move to a

payment system based on quality and outcomes. Continued use of an outdated and broken coding system erodes data quality and, thus, has an adverse effect on the value of health care data, including an increased risk for inaccurate health care decisions based on faulty and imprecise data. The ability to accurately analyze health care services provided to patients and whether care is fairly reimbursed is compromised.

Continued use of ICD-9-CM results in costs associated with:

- Inaccurate decisions or conclusions based on faulty or imprecise data
- Administrative inefficiencies because of reliance on manual processes
- Coding errors related to code ambiguity and outdated terminology
- Worsening imprecision in the ICD-9-CM code set because of the inability of the code structure to adequately accommodate desired modifications[4]

OPPORTUNITIES FOR LEVERAGING ICD-10 TO IMPROVE CARE AND REDUCE COSTS

The transition to ICD-10-CM and ICD-10-PCS (collectively referred to as "ICD-10") presents an opportunity to greatly improve the capture of information about the increasingly complex delivery of health care, leading to improvements in health care delivery and operations, better patient outcomes, and reduced health care costs. ICD-10 is the next-generation coding system that will modernize and expand the capacity of health care organizations to keep pace with changes in medical practice and health care delivery by providing higher-quality information for measuring service quality, outcomes, safety, and efficiency. The granular level of detail in ICD-10 codes is expected to generate more precise and clinically accurate characterizations of patient diagnoses, which in turn will lead to a more accurate reflection of patient conditions. The improved structural flexibility will allow for the addition of new diseases or expanded detail in the future.

Measures of health care are only meaningful if the data used to define conditions and services accurately represent the reality of care.[5] Increased precision in ICD-10 will lead to better quality measures. Better and more effective quality measures will translate to better care that will ultimately benefit consumers. The additional detail in ICD-10 will affect analytic tools, reports, and comparative data used by all quality measurement systems, including quality indicators from The Joint Commission, CMS, and the Agency for Healthcare Research and Quality, as well as clinical registries and state reporting systems.

By allowing for greater coding accuracy and specificity, ICD-10 is key to collecting the information needed to implement health care delivery innovations such as patient-centered medical homes and value-based purchasing. The investments that are being made in accountable care organizations (ACOs), meaningful use EHRs, and value-based pur-chasing are all predicated on having a more precise and comprehensive code set that is up to date with the rapid changes in practices and technologies utilized in today's health care system. ICD-10 will enable better patient care through better understanding of the value of new procedures, improved disease management, and an improved ability to study and understand patient outcomes, yielding benefits to patients far beyond cost savings. Better understanding of diseases and injuries will lead to improved prevention or mitigation strategies. Clinically robust algorithms to treat chronic diseases and track outcomes of care can be designed.

New models of health care payment and patient management, such as ACOs, bundled payments for episodes of care, pay for outcomes, risk sharing for total costs of care, and patient-centered medical homes will create increased demand for detailed, high-quality data. Accurate, detailed health care data will be needed to construct risk analyses and predictive models that allow rational risk sharing. Patient populations need to be defined, care paths assessed, and care outcomes understood much more clearly and deeply than they are today if payers, employers, and providers are to negotiate as equals. Additionally, information that drives regional or national health care policies relies on intelligence derived from coded data. Decisions are only as good as the information those decisions are based on. Better data will translate to better decisions.[5]

EHRs and interoperability require a modern code set for summarizing and reporting data. Without ICD-10, the U.S. investments in EHRs is greatly diminished, as the value of more comprehensive and detailed health information is lost if it is aggregated into outdated, broad, ambiguous codes. The health care industry has struggled to define health information standards that will allow true interoperability and the ability to analyze "big data" across enterprises.[5] ICD-10 is needed to exchange meaningful data. Also, many public and national health information systems, reporting programs, and data sets rely on accurate and timely diagnosis codes to classify and track disease morbidity and mortality, quality of care, and health disparities, and monitor public health threats. Use of ICD-10 will standardize the reporting of public health data (including disease outbreaks and bioterrorism events) across the globe, achieve international health data comparability, and enable international comparisons of quality of care and sharing of best practices among countries.

Since ICD-10 has been used for mortality reporting in the United States since 1999, the implementation of ICD-10 for morbidity reporting would achieve comparability between mortality and morbidity data, resulting in enhanced data for improving community health and administrative cost savings. In many states, mortality data are cross-analyzed with hospital data to develop intervention strategies. Resources are being wasted to convert mortality data back to ICD-9-CM to correlate with hospital data.

Anticipated benefits of using more robust, up-to-date code sets can be identified in the following areas[6]:

Quality measurement

- Better data for evaluating and improving quality of care
- Reduction in complications and improved patient safety
- Improved patient outcomes
- Greater ability to measure outcomes, efficacy, and costs of new medical technology
- Greater ability to ascertain disease severity for risk and severity adjustment
- Greater ability to manage chronic diseases

Public health

- Enhanced public health surveillance
- Greater ability to track and respond to global health threats
- Facilitate international comparisons of quality of care and global sharing of best practices

Research

- Code analysis is essential to research when direct access to patient records is not possible
- Data could be used in more meaningful ways to enable better understanding of complications, better design of clinically robust algorithms, and better tracking of the outcomes of care
- Greater detail offers the ability to discover previously unrecognized relationships or uncover phenomenon such as an incipient epidemic early
- Expanded injury research and successful injury prevention strategies
- Organizational monitoring and performance
- Administrative efficiencies
- Cost containment
- More accurate trend and cost analysis
- Improved ability to analyze trend and cost data
- More effective monitoring of resource and service utilization
- Reduced submission of medical record documentation to support reimbursement claims
- Reduced reliance on manual medical review
- Improved coding accuracy and productivity

Reimbursement

- More accurate and fair reimbursement
- Better justification of medical necessity
- Fewer erroneous and rejected claims
- Increased sensitivity when making refinements in applications, such as grouping and reimbursement methodologies
- Reduced opportunities for fraud and improved fraud detection capabilities

Health information technology

- Realize benefits of SNOMED-Clinical Terms and interoperable health data exchange
- Facilitate electronic data retrieval
- Expanded computer-assisted coding technologies

Health policy and strategy

- Improved information for setting health policy
- Better data for operational and strategic planning

- Better data for designing health care delivery

ICD-10 can be viewed as the hub of a number of major health information technology initiatives (Fig. 2).[7]

ICD-10 BENEFITS FOR PATIENTS AND CONSUMERS

The higher-quality health information produced by ICD-10 will benefit patients and consumers. Although clinical research in controlled studies is invaluable, it is necessary to have standard and universally available data across all health care settings to assess health care delivery across providers, payers, populations, and regions. Today, that data primarily come from coded data reported on reimbursement claims.

Better information around metrics such as risk, complexity, comorbidities, complications, sequelae, severity, health care–associated conditions, safety, and effectiveness of treatment is essential for improving our health care delivery system, properly allocating resources, and ultimately improving patient care. The more specific the diagnostic information is, the easier it is to identify the best treatment and avoid potential complications. Greater detail also offers the ability to discover previously hidden relationships or uncover phenomena such as an incipient epidemic early. ICD-10 provides much more detail about adverse clinical events and medical device complications, allowing better identification and tracking of these occurrences so that more effective strategies can be developed to reduce the incidence and clinical consequences of these events. Not only will better data lead to improved care of the individual patient, but the health of populations locally, regionally, and nationally will also be improved.

Improved diagnostic data will permit improved identification of patients for disease management programs and more effective tailoring of these programs to meet individual patient needs, thus, improving patient outcomes, patient satisfaction, and lowering health care costs. ICD-9-CM codes describe many chronic diseases in general terms, whereas

FIGURE 2. ICD-10 and Health Information Technology Initiatives

Abbreviations: ICD, International Classification of Disease; ACO, accountable care organization.

ICD-10 recognizes distinctions in clinical conditions and severity that can help segment patient populations within a disease category. ICD-10 offers opportunities for improved, automated identification, stratification, and segmentation of patient populations. With greater code specificity, better algorithms can be developed to identify and target-specific patient populations and subpopulations for disease management programs and customize programs for patients with differences in severity or risk. Target groups' progress toward goals and effectiveness of treatment can be monitored through the clinical and severity distinctions in ICD-10 codes. As more ICD-10 data is collected and additional ICD-10 experience is gained, prediction models can be greatly enhanced to more accurately predict risk within populations by a number of refined parameters. Superior data will improve the ability to evaluate the effectiveness of disease management programs in improving patient outcomes, reducing the incidence of acute episodes, and decreasing health care costs.

Ultimately benefiting patients, better data will support:

- Improvements in patient outcomes and patient safety through better data for analysis and research
- Improved ability to manage chronic diseases by better capturing patient populations
- More accurate reflection of patients' clinical complexity and severity of illness
- Improved ability to identify high-risk patients who require more intensive resources
- Improved ability to manage population health
- Improved information sharing, which can enhance treatment accuracy and improve care coordination
- Improved ability to assess effectiveness and safety of new medical technology
- Improved diagnosis of chronic illness and identification of underlying causes, complications of diseases, and conditions that contribute to disease complexity
- More accurate reflection of clinical complexity and severity of illness
- Increased patient engagement

Complete and accurate data must be reported to put the most appropriate picture of the quality of care delivery in front of increasingly sophisticated and informed potential patients. With better data will come an expanded ability to educate consumers on costs and outcomes of treatment options. Increased patient understanding and involvement in their health care will improve the population's health and decrease the cost of health care.

ICD-10 BENEFITS FOR CLINICIANS

The transition to ICD-10 also benefits clinicians. Compared with ICD-9-CM, medical terminology and classification of diseases are more consistent with current clinical practice and medical knowledge (e.g., newly recognized conditions are identified and conditions with a recently discovered etiology have been reclassified). Many physician specialty societies have actively contributed to the clinical content of ICD-

10-CM/PCS and continue to be involved in the annual updating process to ensure the code sets represent current clinical knowledge. The increased specificity will provide better justification of medical necessity for treatment and diagnostic tests. Exchange of patients' clinical information will be more efficient. Better data on patients' clinical conditions will help to validate reported evaluation and management codes and result in less misinterpretation by auditors, attorneys, other third parties. More detailed data facilitates the informed use of both business intelligence and clinical dashboards. Business intelligence dashboards make performance and trend data more readily available and, thus, facilitate attainment of meaningful use criteria. Clinical dashboards have the potential to drive better care paths and achieve better clinical outcomes.

The increased granularity of ICD-10 will enable more directed clinical decision support. When a patient has multiple medical conditions or manifestations of a condition, the failure of clinical decision support to take into account all of the patient's clinical factors can result in: (1) lack of oversight or specific monitoring of manifestations and (2) medication protocols and their effect on the patient during and after treatment. The ability to fully leverage clinical decision support tools will help direct clinician monitoring to avoid complications or adverse drug events.

In an accountable care environment, providers need to assume an essential role in determining and prioritizing those services that offer the greatest benefit in the context of financial constraints. Models that allow providers who are part of integrated delivery systems to take on the risk of care delivery and share the rewards of high-quality, efficient care are continuing to evolve. The ability of ICD-10 to provide better detail to define risk, severity, anatomic detail, comorbidities, complications, disease phases, sequelae, and other key parameters of the patient's health state will be critically important in effectively managing patients and benefiting from efficient care delivery.[5]

The move to ICD-10 will also lead to increased administrative efficiencies and, thus, lower administrative costs. These reduced administrative costs come from improved coding accuracy and productivity, fewer pended or denied reimbursement claims because of more information provided by the submitted codes, and fewer payer requests for submission of supporting medical record documentation (because of more detailed information provided by the codes). The increased specificity, representation of current clinical knowledge, and use of more up-to-date medical terminology will make ICD-10 codes easier to assign than ICD-9-CM codes. In the long-term, after the learning curve has ended, it is expected that the use of ICD-10 will result in fewer coding errors than ICD-9-CM because ICD-10 is less ambiguous and more logically organized. The ambiguity in ICD-9-CM and use of outdated terminology that does not correspond to terms used in clinical documentation makes ICD-9-CM confusing, difficult to use, and open to misinterpretation. The increased specificity in ICD-10 will also facilitate the development of more sophisticated automated coding tools to as-

sist with proper code selection, thereby, improving coding accuracy and compliance with payment policies, increasing administrative efficiencies, and reducing manual labor involved in the coding process. For all of these reasons, coding productivity is expected to improve over time, once the learning curve to become familiar with the new codes has ended. In fact, computer-assisted coding technology may increase coder productivity by as much as 30% to 50%.[8]

umentation led to the inclusion of the expanded detail and specificity in ICD-10. Since precise medical record documentation is critical to support ICD-10 codes, the transition to ICD-10 can help to achieve high-quality documentation by advancing documentation assessment and improvement efforts. Ensuring high-quality documentation and thorough coder preparation minimizes the adverse effects of the ICD-10 transition on coding accuracy and productivity, which in turn reduces the potential for rejected claims and payment errors.

LEVERAGING TECHNOLOGY TO IMPROVE CLINICAL DOCUMENTATION

The transition to ICD-10 presents opportunities for innovations in improving the quality of clinical documentation while minimizing the burden of documentation capture on clinicians. For example, technology can be leveraged to facilitate documentation capture at the point of care (such as the use of prompts or templates in EHRs). Mobile devices can be used to provide physicians with customized lists of documentation tips.

High-quality documentation is increasingly in demand to support many emerging health care initiatives aimed at improving care and reducing costs. Growing demands for more detailed diagnostic data generated from medical record doc-

BENEFITS OF ICD-10 PREPARATION IN ADVANCE OF TRANSITION

Many ICD-10 preparation activities can provide value in advance of the transition to ICD-10. Clinical documentation is necessary for supporting many health care initiatives, including improving the quality of care, lowering health care costs, measuring mortality risk and severity of illness, analyzing readmission rates, and meeting meaningful use requirements. Also, high-quality documentation will help improve today's ICD-9-CM coding accuracy. Accurate and complete documentation is important for good patient care regardless of the code set in use. ICD-10 education has been shown to improve ICD-9-CM coding accuracy, as basic coding principles are reinforced and foundational knowledge in biomedical sciences is strengthened.[6]

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CENTRAL NERVOUS SYSTEM TUMORS

Brain Metastases: From Clinical Trials to Clinical Practice

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Targeted and Immunotherapeutic Approaches in Brain Metastases

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OVERVIEW

Brain metastases are a common and devastating complication of cancer. The approach to the management of brain metastases is often multidisciplinary and includes surgery, whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and systemic therapeutic agents. Until recently, systemic therapy has had a limited role in the management of brain metastases because of a lack of activity, challenges of blood-brain barrier penetration, the heterogeneous patient population, and a heavily pretreated patient population. Advances in the understanding of the biology of brain metastases and molecularly defined disease subsets have facilitated an emerging role of novel therapeutic agents, including targeted therapies and immunotherapy, in the management of brain metastases.

Brain metastases are serious complications of systemic cancer that occur in 10% to 30% of adults with cancer.[1] The most common malignancies that metastasize to the brain are lung, breast, and melanoma.[2-5] Eighty percent of patients present with brain metastases within the cerebral hemispheres; 15% are within the cerebellar hemispheres and 5% are within the brainstem.[6] Key determinants in the management of brain metastases include the tumor histology, number, size, and site of lesions; the status of extracranial metastases; and the performance status of the patient. One of the challenges in the development of effective therapies for brain metastases is the presence of the blood-brain barrier, a highly selective permeability barrier made of capillary endothelial cells connected by tight junctions and astrocyte foot processes that limit entry of systemic therapies into the brain.[7,8] In addition, active transport mechanisms of drug efflux and high plasma protein binding of agents further lower the volume of distribution of agents in the brain parenchyma.[8] An additional challenge is that patients who develop brain metastases often are heavily pretreated with tumors that are more likely to be resistant to therapy at diagnosis of the brain metastases. The role of systemic therapy (chemotherapy, targeted agents, or immunotherapy) in brain metastases is not well defined, because there is no level-1 evidence favoring the use of systemic therapy compared with local approaches. However, in recent years, the development of novel cytotoxic agents and targeted therapies with better blood-brain barrier penetration have increased the interest in use of systemic therapies in brain metastases.

TARGETING BRAIN HOST CELLS

Another potential mechanism of resistance in metastatic tumor cells in the brain is their interaction with brain resident cells. The brain metastatic process depends on the perpetuation of a perivascular niche, at least during the early steps,[9] and this niche has been associated with promotion and/or maintenance of a stem-like and resistant cellular phenotype, per se, in brain tumors. The components of the blood-brain barrier (endothelial cells, pericytes, astrocytic foot processes, and/or the vascular basement membrane)[10] are likely candidates to provide this supportive niche for cancer cells. Conversely, the high inefficiency of the brain metastatic process (with 95% to 99% of brain-arrested cancer cells failing to successfully grow to a macrometastasis[9]) raises the question of whether some of these components are more foe than friend for extravasating cancer cells in the brain. A recent report suggested that the astrocyte-produced plasminogen activator forces brain metastatic cancer cells into apoptosis and that cancer cells need to inhibit this process to survive this brain protective mechanism.[11] In contrast, astrocytes might protect brain metastatic cancer cells from the adverse effects of chemotherapy by buffering intracellular calcium increases via gap junction coupling and other mechanisms.[12] Thus, the role of many brain resident cells appears to be complex, and further research is required to understand the potential to target them for brain metastasis prevention or treatment. The brain endothelial cell (the main cell type reacting to angiogenic growth factors produced by tumor cells) appears to be among the most promising cellular target that is emerging, as detailed in this review.

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TARGETING ANGIOGENESIS

Preclinical data from multiple animal models support the potential role of antiangiogenic agents for the prevention and treatment of brain metastases. Elevated vascular endothelial growth factor (VEGF) expression has been linked to the development of brain metastasis in a murine model.[13] Kim et al[14] showed that treatment with a VEGF receptor tyrosine kinase inhibitor reduced angiogenesis and restricted the growth of brain metastasis in a murine breast cancer model.[14] In another mouse model, inhibition of VEGF signaling using bevacizumab efficiently inhibited angiogenesis-dependent macrometastases formation of brain-metastasizing lung adenocarcinoma cells, arresting micrometastases in a chronic dormant state.[9] However, the growth pattern of different tumor (sub-)types in the brain is highly different; for example, lung carcinoma is highly angiogenesis dependent, and melanoma is less dependent on angiogenesis (because of the ability to grow co-optively along pre-existing brain microvessels[9]). These preclinical observations support the clinical evaluation of antiangiogenic agents in brain metastases therapy and prevention. Antiangiogenic agents (e.g., those targeting the VEGF pathway) have to reach only the endothelial cell to inhibit ligand-receptor interactions and may not need to fully cross the blood-brain barrier. Initial experience with bevacizumab in six patients who had non–small cell lung cancer (NSCLC) with brain metastases was shown to be safe and resulted in a partial response in two patients,

stable disease in three patients, and disease progression in one patient.[15] Initial safety concerns about the risk of bleeding in the brain with such agents have not been supported by reported experience.[16] A phase II trial of bevacizumab in combination of carboplatin showed an overall response rate in the central nervous system (CNS) of 45% by RECIST.[17] An initial report of a phase II study of cisplatin, etoposide, and bevacizumab demonstrated a response rate of 60% in patients who have breast cancer with brain metastases.[18] These high response rates with bevacizumab may be a result of pseudoresponse (decrease in contrast enhancement on MRI because of the antipermeability effect of bevacizumab on the vasculature) and not necessarily an antitumor effect.[19]

TARGETING EPIDERMAL GROWTH FACTOR RECEPTOR AND ANAPLASTIC LYMPHOMA KINASE IN LUNG CANCER WITH BRAIN METASTASES

Approximately 40% to 50% of patients who have locally advanced NSCLC will develop brain metastases.[20] Activating mutations in the epidermal growth factor receptor (*EGFR*) occur in approximately 10% to 15% of NSCLC. Multiple small-molecule tyrosine kinase inhibitors, such as erlotinib, gefitinib, and afatinib, are U.S. Food and Drug Administration (FDA) approved for the treatment of lung cancer with *EGFR* mutations. An *EGFR* inhibitor, such as erlotinib, can serve as a potential radiation sensitizer to increase the efficacy of the radiation. In a phase II study of 40 patients who had NSCLC with brain metastases, the combination of whole-brain radiation therapy and erlotinib was reported to be safe (no reported increase in neurotoxicity).[21] The median survival time was 11.8 months for the whole cohort. The overall survival (OS) time was 19.1 months in the patients with mutant *EGFR* compared with an OS time of 9.3 months in the patients with wild-type *EGFR* (Table 1).[21] However, a phase III trial (RTOG 0320) failed to show any additional benefit of erlotinib in combination with WBRT and stereotactic radiosurgery (SRS) in patients who had brain metastases from NSCLC.[22] However, one limitation of the study was that patients were not stratified according to *EGFR* mutational status. In a large cohort of 110 patients who had *EGFR*-mutant lung cancer with newly diagnosed brain metastases, patients treated with WBRT (32 patients) had a longer median time to intracranial progression than the 63 patients who received erlotinib as up-front therapy (24 vs. 16 months).[23] Patients treated with erlotinib or SRS experienced intracranial failure as a component of first failure more often, whereas patients who received WBRT experienced failure outside the brain more often. The OS was similar between the WBRT and erlotinib groups; patients treated with SRS initially had a longer OS than those who received erlotinib. In a phase II study of 41 patients who had NSCLC (unselected for *EGFR* mutation), treatment with gefitinib resulted in an objective response rate of 10% in the brain.[24] Higher response rates with *EGFR* inhibitors have been reported in studies that are enriched with pa-

KEY POINTS

- A multidisciplinary approach involving the neurosurgeon, medical oncologist, neuro-oncologist, and radiation oncologist is recommended in the management of brain metastases.
- A number of agents that target epidermal growth factor receptor and anaplastic lymphoma kinase mutations have been effective in the treatment of brain metastases that harbor these mutations.
- The greatest advances in the systemic treatment of breast cancer brain metastases have been made in patients who have *HER2*-positive disease.
- Small-molecule tyrosine kinase *BRAF* inhibitors that target *BRAF*^V600-mutant melanoma have demonstrated activity in active melanoma brain metastases. Ipilimumab is an immunotherapeutic agent that has demonstrated activity in a prospective, phase II trial conducted in patients who have melanoma with asymptomatic brain metastases. (Patients who did not require corticosteroid therapy had a better response than those who needed corticosteroids because of brain edema.)
- There is a need for prospective clinical trials to test new combinations of targeted and immunotherapeutic agents with local therapies to address the optimal sequencing of local and systemic therapies in the management of brain metastases.

TABLE 1. Selected Clinical Trials with Targeted Agents and Immunotherapy in Brain Metastasis

Study	Year	Study Design	Patient Population	Therapeutic Intervention	No. of Patients	Median PFS (Months)	Intracranial RR (%)	Median OS (Months)
Ceresoli et al[24]	2004	Phase II	New and recurrent NSCLC- BM	Gefitinib	41	3	27	5
Wu et al[69]	2007	Single arm, phase II	New and recurrent NSCLC- BM	Gefitinib	40	9.0	32	15.0
Sperduto et al[22] (RTOG-0320)	2013	Three arm, phase III	New NSCLC-BM	WBRT + SRS	44	8.1	–	13.4
				WBRT+ SRS + temozolomide	40	4.6	–	6.3
				WBRT + SRS + erlotinib	41	4.8	–	6.1
Welsh J et al[21]	2013	Single arm, phase II	New NSCLC-BM	WBRT + erlotinib	40	8.0	86	11.8
Lee et al[70]	2014	Phase II, double blind, placebo controlled	New NSCLC-BM	WBRT	40	1.6	–	2.9
				WBRT + erlotinib	40	1.6	–	3.4
Long et al[48] (BREAK-MB)	2012	Open label, two cohort, phase II	New and recurrent *BRAF*-positive MBM	Dabrafenib	Cohort A, V600E (new): 74	4.0	39.2	8.2
					Cohort A, V600K (new): 15	2.0	6.7	4.0
					Cohort B, V600E (recurrent): 65	4.1	30.8	7.8
					Cohort B, V600K (recurrent): 18	4.0	22.2	5.4
Kefford et al[51]*	2015	Open label, two cohort, phase II	New and recurrent *BRAF*-positive MBM	Vemurafenib	Cohort 1 (recurrent): 90	4.0	18	7.0
					Cohort 2 (new): 56	4.3	20	6.9
Bachelot et al[40] (LANDSCAPE)	2013	Open label, phase II	HER2+ BCBM	Lapatinib + capecitabine	45	5.5 months (TTP)	66	17
Lin et al[71]	2009	Phase II	HER2+ BCBM	Lapatinib	242	2.4 months	6	6.4

Abbreviations: PFS, progression-free survival; RR, response rate; OS, overall survival; NSCLC-BM, non-small cell lung cancer brain metastases; WBRT, whole-brain radiation therapy; SRS, stereotactic radiotherapy; MBM, melanoma brain metastases; BCBM, breast cancer brain metastasis; TTP, time to tumor progression.
*Preliminary results.

tients who have known *EGFR* mutations.[25,26] In a phase II study, treatment with erlotinib or gefitinib resulted in partial response rate of 83% and a disease control rate of 93% in 28 patients who had *EGFR*-mutant NSCLC with brain metastases.[25] A recent pooled analyses also strongly suggests that EGFR tyrosine kinase inhibitors are an effective treatment for patients who have NSCLC with brain metastases.[27] Erlotinib appears to achieve higher cerebrospinal fluid concentrations than gefitinib.[28]

Approximately 2% to 7% of patients who have NSCLC harbor rearrangements in the anaplastic lymphoma kinase *(ALK)* gene that encodes a cytoplasmic chimeric protein with constitutive kinase activity.[29] Crizotinib is an oral kinase inhibitor approved for the treatment of *ALK*-rearranged NSCLC. An analysis of 275 patients with asymptomatic brain metastases who were randomly assigned to the crizotinib arm in the PROFILE 1005 or 1007 studies included 109 patients who were radiation naive and 166 patients who had received prior brain radiotherapy.[30] The systemic disease control rate (DCR) at 12 weeks was 63%, the intracranial DCR was 56%, and the median intracranial time to progression (TTP) was 7 months in the radiation-naive group. In the cohort of patients who had previous radiation therapy, the systemic DCR was

65%, the intracranial DCR was 62%, and the median intracranial TTP was 13.2 months.

TARGETING HER2 IN BREAST CANCER BRAIN METASTASES

An estimated 10% to 30% of all patients with breast cancer will eventually develop brain metastases.[31] The greatest advances in systemic treatment of brain metastases in patients with breast cancer have been made in patients with *HER2*-positive disease primarily because of the advent of efficacious *HER2*-directed agents. Approximately one-third of patients who have advanced *HER2*-positive breast cancer develop brain metastasis, which is responsible for death in half of these patients.[32,33] Large monoclonal antibody agents, such as trastuzumab, trastuzumab-emtansine (T-DM1), and pertuzumab, may not penetrate the blood-brain barrier. However, PET imaging data in a limited number of patients using [89]Zr-trastuzumab have demonstrated CNS uptake of trastuzumab into brain metastases, which suggests an ability of trastuzumab to cross a disrupted blood-brain barrier.[34] There is some evidence that these patients may derive additional benefit with the continuation of trastuzumab after development of breast

cancer brain metastasis.[35] There are multiple cases of *HER2*-positive breast cancer with brain metastasis that show a CNS response to T-DM1.[36,37]

Lapatinib, a small-molecule tyrosine kinase inhibitor of *HER1* and *HER2*, is FDA approved for metastatic HER2-positive breast cancer after progression occurs during treatment with trastuzumab in combination with capecitabine. There is preclinical evidence that lapatinib has activity in *HER2*-positive breast cancer with brain metastasis in mouse models that led to clinical trials of lapatinib in HER 2-positive breast cancer with brain metastasis (Table 1).[38] However, in a phase II study of 242 patients who had HER2-positive breast cancer and progressive brain metastases (after radiation), monotherapy with lapatinib resulted in an intracranial response rate of 6%.[39] During disease progression in the same study, 10 of the 50 patients (20%) who received a combination of lapatinib and capecitabine showed an objective response in the brain. In the LANDSCAPE study, a combination of lapatinib plus capecitabine in previously untreated patients with HER2-positive breast cancer with brain metastasis resulted in an objective CNS response in 29 of the 45 patients (66%) and a median time to CNS progression of 5.5 months.[40]

There are number of ongoing studies (Table 2) on HER2-positive breast cancer with brain metastasis that include the cooperative-group randomized, phase II study of WBRT with or without lapatinib in patients who have HER2-positive breast cancer with brain metastasis. This study (NCT01622868) evaluates lapatinib as a radiosensitizer in combination with WBRT.[41] Other HER2-directed therapies under active investigation in breast cancer with brain metastases include the irreversible HER2 inhibitors neratinib (NCT01494662)[42] and afatinib (NCT01441596).[43] ARRY-380, a HER2-selective inhibitor with some ability to cross the blood-brain barrier and activity in intracranial tumor mod-els, is undergoing evaluation in combination with trastuzumab (NCT01921335).[44]

TARGETING *BRAF* IN MELANOMA BRAIN METASTASES

Brain metastases are a substantial problem in melanoma and occur in up to 50% of patients with metastatic melanoma.[45] Activating *BRAF* mutations that result in constitutive activation of the mitogen-activated protein kinase pathway occur in 40% of patients with melanoma. More than 95% of *BRAF* mutations are the V600E mutation (substitution of valine by glutamic acid at the 600th amino acid position). Other mutations seen in melanoma include *NRAS* (20%) and *KIT* (2%). Patients who harbor these mutations may be at a higher risk for developing brain metastases, as demonstrated in a study in which 24% and 23% of patients who had stage IV melanoma and *BRAF* and *NRAS* mutations, respectively, had CNS involvement at the time of diagnosis, compared with 12% of patients who did not harbor these mutations.[46]

Promising initial activity was seen in 10 patients with untreated, asymptomatic brain metastases who were enrolled in the phase I study of dabrafenib, a BRAF inhibitor. There were four brain complete responses and four brain partial responses.[47] This led to the open-label phase II study, BREAK-MB (*BRAF*-mutant melanoma metastatic to the brain). In this trial, 172 patients who had V600E or V600K mutation–positive melanoma brain metastases received dabrafenib monotherapy.[48] Eighty-nine patients in cohort A were naive to local therapy (no prior local therapy), and 83% of patients in cohort A and 78% (65 of 83 patients) in cohort B had *BRAF*^{V600E}-mutant melanoma. This study demonstrated the activity of a *BRAF* inhibitor in patients who had *BRAF*^{V600E}-mutant melanoma metastatic to the brain, irrespective of prior local therapy. The response rates were lower

TABLE 2. Selected Ongoing Clinical Trials of Targeted and Immunotherapeutic Agents in Brain Metastasis

Intervention	Phase	Primary Malignancy	Target	Anticipated Enrollment (No. of Patients)	CT No.
WBRT vs. erlotinib + WBRT[72]	III	NSCLC	*EGFR*	224	NCT01887795
Veliparib + WBRT vs. WBRT[73]	II	NSCLC	PARP	307	NCT01657799
Pembrolizumab[63]	II	Melanoma and NSCLC	PD-1	64	NCT02085070
Radiation + ipilimumab[74]	II	Melanoma	CTLA-4	66	NCT02115139
Vemurafenib[75]	II	Melanoma	*BRAF*	34	NCT01781026
Dabrafenib[49]	II	Melanoma	*BRAF*	39	NCT01721603
Nivolumab + ipilimumab[76]	II	Melanoma	PD-1/CTLA-4	148	NCT02320058
Everolimus + trastuzumab + vinorelbine[77]	II	Breast	*HER2*	35	NCT01305941
BKM 120 + trastuzumab[78]	II	Breast	*HER2*/PI3K	72	NCT01132664
WBRT ± lapatinib[41]	II	Breast	*HER2*	143	NCT01622868
HKI-272 (neratinib)[42]	II	Breast	*HER2*	105	NCT01494662
Afatinib[43]	II	Breast	*HER2*	121	NCT01441596
ARRY-380 + trastuzumab[44]	I	Breast	*HER2*	50	NCT01921335

Abbreviations: CT, clinical trials; WBRT, whole-brain radiation therapy; NSCLC, non-small cell lung cancer; PARP, poly(ADP-ribose) polymerase; PD-1, programmed cell death protein 1; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; PI3K, phosphatidylinositol 3-kinase.

in patients in cohort B who had progressive brain metastases after some initial local therapy (surgery, WBRT, and SRS). Dabrafenib therapy resulted in a 39% intracranial response rate (29 of 74 patients in those with V600K mutations); 7% (one of 15 patients) and 22% patients (four of 18 patients) in cohorts A and B, respectively, achieved intracranial response. There is an ongoing study of dabrafenib in combination with SRS in $BRAF^{V600E}$-mutated metastatic melanoma (NCT01721603).[49]

In an open-label pilot study, 24 patients who had $BRAF^{V600}$ mutation–positive melanoma with brain metastases were treated with vemurafenib, a $BRAF$ inhibitor. Three of 19 patients who had measurable brain disease achieved a partial response, and seven of 19 patients (37%) achieved at least 30% tumor regression.[50] A phase II trial of 146 patients who had $BRAF^{V600}$ mutation–positive melanoma with active brain metastases and who were treated with vemurafenib was recently reported.[51] Cohort 1 consisted of 90 patients without any prior local treatment for brain metastases, and cohort 2 included 56 patients who had progressive brain metastases after prior local therapy. Vemurafenib resulted in intracranial objective response rates of 18% (16 of 90 patients) and 20% (11 of 56 patients) in cohorts 1 and 2, respectively. The median progression-free survival and OS were similar in both cohorts (3.7 and 6.5 months, respectively, in cohort 1, and 4.0 and 6.4 months, respectively, in cohort 2).

IMMUNOTHERAPY IN MELANOMA BRAIN METASTASES

Traditionally, the CNS was considered an immunologically privileged site because of the restriction of the conventional circulation of lymphocytes and antibodies by the blood-brain barrier. Recently, though, the concept of immunologic privilege in the CNS has been refuted.[52] There is evidence that activated T cells can patrol the CNS in an antigen-independent and unrestricted manner and then return to the systemic circulation.[53] Several studies have confirmed that T cells can cross the blood-brain barrier,[54] thereby supporting the strategy of T-cell responses as an antitumor approach.[55]

Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) is an inhibitory immune checkpoint that downregulates T-cell proliferation. Blockage of CTLA-4 results in T-cell proliferation and an associated immunologic response, leading to interleukin-2 production and cytotoxic activity.[56] Ipilimumab is a monoclonal antibody against CTLA-4 that has showed activity in patients who have melanoma with brain metastases. Eighty-two patients with stable brain metastases off corticosteroids were enrolled in MDX-020, a randomized, double-blind, and placebo-controlled trial of ipilimumab plus gp100 versus ipilimumab alone versus gp100 glycoprotein vaccine.[56] The toxicity profile of ipilimumab in these patients was similar to that seen with other studies, and there were no additional safety concerns.

This led a phase II study of 72 patients who had melanoma with brain metastases and who were treated with ipilimumab.[57] The patients were divided in two cohorts depending on corticosteroid use and age: cohort A included 51 patients who had asymptomatic brain metastases, and cohort B included 21 patients who were neurologically symptomatic and receiving corticosteroids. Some patients had received prior brain radiotherapy. Global disease control (defined as complete response or partial response or stable disease) after 12 weeks as assessed by modified World Health Organization criteria was seen in 18% (nine of 51 patients) in cohort A and in 5% (one of 21 patients) in cohort B. Using the immune-related response criteria, the response rates were 24% (13 of 51 patients) and 10% (two of 21 patients) in cohorts A and B, respectively. Eight of 51 patients in cohort A had a partial response, and four had stable disease, which provided a disease control rate in the brain of 23.5%. The response rate in cohort B was lower, with one patient each having a partial response or stable disease in brain. The median OS and the 24-month survival rate were 7.0 months and 26%, respectively, in cohort A and 3.7 months and 10%, respectively, in cohort B.

A phase II study of ipilimumab in combination with fotemustine included 20 patients who had asymptomatic brain metastases. This study showed intracranial disease control in 50% of patients who had melanoma with brain metastases (10 patients). Five patients had stable disease or a partial response, and five patients had a complete response.[58]

Anti-programmed cell death protein 1 (PD-1) antibodies are checkpoint inhibitors that block the interaction between the PD-1 receptor, expressed on T cells, and a ligand, programmed death ligand 1 (PD-L1), expressed on tumor cells and resulting in inactivation of T cells at the tumoral level and augmenting the antitumor immune response. Two agents in this class, nivolumab and pembrolizumab, have shown promising activity and some durable responses in metastatic melanoma.[59-62] There is an ongoing phase II study of pembrolizumab in patients who have brain metastases from NSCLC and melanoma (NCT02085070).[63]

OUTLOOK: FROM TREATMENT TO PREVENTION

The advent of targeted therapies has facilitated the transition from the previous practice of treating brain metastasis according to a rather crude algorithm,[64] which at times did not take into consideration the histologic tumor type, to a more rational treatment approach based on individual tumor characteristics. Patients with brain metastases have long been systematically excluded from clinical trials, although there is a growing recognition in the physician community that there is no rationale to continue to do so.[65] We expect the development of more trials that focus on systemic targeted therapies in brain metastases in the future. Such studies should implement molecular stratification factors whenever possible. Basic and translational investigations are needed to identify novel molecular targets and also to understand secondary resistance mechanisms that are likely to limit lasting effects of many targeted drugs. The use of RECIST to measure the tumor response of molecularly targeted agents may underestimate their effectiveness, because prolonged tumor stabilization is a common finding with some of these agents.

However, the potential of targeted agents (like classical chemotherapy) to prevent metastases, including brain metastases, has rarely been systemically addressed.[66,67] In general, clinical trials are not (yet) designed to prospectively investigate the rate of metastasis formation. Given that the vast majority of patients with cancer die from metastatic disease and not from the primary tumor, and given that brain metastases constitute a most serious neurologic complication of cancer, brain metastasis is an important area for future preclinical and clinical cancer research.[68] Targeted therapies are excellent candidates for such brain metastases prevention studies; they often can be given to patients over prolonged periods of time with good tolerability.

CONCLUSION

A multidisciplinary strategy is recommended for the individualized management of brain metastases for every patient. An approach that includes surgery, WBRT, SRS, or systemic therapy, or a combination of these modalities, often is advocated on the basis of the performance status, age, tumor type, number of metastases, and extracranial disease status of patient. There is emerging data that targeted agents and immunotherapeutic approaches have activity in the brain, which is likely to develop a significant impact on the intracranial disease. The optimal timing of systemic therapies (therapeutic or prophylactic) remains to be determined.

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Whole-Brain Radiotherapy and Stereotactic Radiosurgery in Brain Metastases: What Is the Evidence?

Minesh P. Mehta, MD, and Manmeet S. Ahluwalia, MD

OVERVIEW

The overall local treatment paradigm of brain metastases, which includes whole-brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS), continues to evolve. Local therapies play an important role in the management of brain metastases. The choice of local therapy depends on factors that involve the patient (performance status, expected survival, and age), the prior treatment history, and the tumor (type and subtype, number, size, location of metastases, and extracranial disease status). Multidisciplinary collaboration is required to facilitate an individualized plan to improve the outcome of disease in patients with this life-limiting complication. There has been concern about the neurocognitive effects of WBRT. A number of approaches that mitigate cognitive dysfunction, such as pharmacologic intervention (memantine) or a hippocampal-sparing strategy, have been studied in a prospective manner with WBRT. Although there has been an increase in the use of SRS in the management of brain metastases in recent years, WBRT retains an important therapeutic role.

One of the first descriptions of WBRT is from Chao et al,[1] who demonstrated a high rate of short-duration palliation. Several subsequent large trials established a significant palliative role for this modality. Borgelt et al[2] demonstrated equivalency between various dose-fractionation schema by reviewing the Radiation Therapy Oncology Group (RTOG) trial outcomes; currently, 30 Gy in 10 fractions and 37.5 Gy in 15 fractions are considered standard doses for WBRT.[2] For almost 5 decades, WBRT has remained the primary modality for the treatment of the vast majority of patients with brain metastases, but, starting in the 1990s, several new treatment refinements have led to the redefinition of its role.

THE PARAMOUNTCY OF LOCAL CONTROL CHANGES THE PARADIGM

After the 1990 study by Patchell, which established a survival benefit from resection of a single metastatic lesion to the brain beyond that of WBRT alone, the next logical question was whether or not WBRT is necessary after resection at all. In 1998, in a randomized study, the addition of WBRT after complete tumor resection decreased intracranial failure from 70% to 18% (p < 0.001) and decreased local recurrence from 46% to 10% (p < 0.001).[3] Although there was improved survival with the use of WBRT, this was not significant, which is an observation worth noting, with the caveat that this study was not powered to assess a survival benefit. Three major di-

rectional thrusts emerged as a consequence of this work: First, in several quarters, WBRT became a routine and accepted standard of care after resection to dramatically and convincingly lower intracranial relapse; second, SRS became widespread as a modality for the local control of at-first limited number of brain metastatic lesions but more recently of multiple lesions; third, the role of WBRT in terms of enhancing local control came under intense scrutiny because of concerns regarding its potential for neurotoxicity and a perceived lack of a survival benefit. The bidirectional evolutionary ramifications of the latter trend were to better understand the mechanisms underlying some of these neurotoxicities and efforts to modulate these through the conduct of innovative clinical trials, as well as to become more selective regarding the application of WBRT primarily for patients who had multiple (with a flexible definition of this concept) brain metastases. This selection often has been in the context of a combined approach with systemic therapeutics, a direction that recently has experienced an upsurge because of the emergence of blood-brain barrier–penetrating agents, primarily in malignancies with driver mutations.

THE EMERGENCE OF RADIOSURGERY AS AN EFFECTIVE LOCAL CONTROL THERAPY

SRS now has become the most widely used focal treatment modality for patients who have brain metastasis. The efficacy

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of SRS for brain metastases was first reported in multiple retrospective studies. Sanghavi et al[4] showed in a retrospective, multi-institutional analysis of 502 patients who were stratified by recursive partitioning analysis (RPA) classes I, II, and III that patients treated with WBRT and SRS compared with WBRT alone had a significant increase in median survival times.[4] The survival times in classes I, II, and III with the combination versus alone were 16.1 versus 7.1 months, 10.3 versus 4.3 months, and 8.7 versus 2.1 months, respectively ($p < 0.05$).[4] RTOG 9508 was a randomized, controlled, phase III trial of 333 patients with one to three brain metastases and a Karnofsky performance score (KPS) of 70 or greater who were treated with WBRT and SRS or WBRT alone.[5] In patients who had a single brain metastasis, treatment with WBRT and SRS compared with only WBRT resulted in a decreased rate of local recurrence at 1 year (18% vs. 29%; $p = 0.01$) and superior median survival times (6.5 vs. 4.9 months; $p = 0.039$). In patients who had two or three brain metastases, local control was significantly improved in the combination arm, but there was no difference in survival time between the two groups. There was an additional benefit in outcomes (maintenance or improvement of KPS and corticosteroid use) in patients who received SRS and WBRT compared with WBRT alone.

The role of SRS alone, without WBRT, was evaluated in subsequent studies. Aoyama et al[6] published a prospective, phase III trial, JROSG 99-1, that randomly assigned 132 patients (mostly with lung cancer) who had a KPS score of 70 or greater and four or fewer metastases to SRS with or without WBRT. The results showed no survival difference (8.0 months for SRS vs. 7.5 months for SRS with WBRT; $p = 0.42$); however, the trial was not powered to detect a significant difference in overall survival and, relative to longer-term survival, there was a nonsignificant survival trend in favor of the WBRT arm (1-year survival rates of 38.5% in the group treated with WBRT plus SRS vs. 28.4% for SRS alone).[6] As anticipated, the study demonstrated that local control rates were improved with the addition of

WBRT to SRS, with a 1-year failure rate of 23.6% for SRS and WBRT compared with 53.2% for SRS only ($p < 0.001$). Two additional randomized trials boosted this data set. The EORTC 22952-26001 study randomly assigned 359 patients to either 30 Gy of WBRT or observation after either surgery or SRS that was performed at the individual discretion of the physicians for patients who had one to three brain metastases. After either surgery or SRS, WBRT was associated with improved local and distant brain control ($p < 0.001$). More robust intracranial control led to less use of salvage therapies and a slightly longer progression-free survival but had no impact on overall survival or survival with functional independence (the primary endpoint of the study). It is important to note that part of the eligibility for the trial required stable systemic disease or asymptomatic primary tumors, thereby attempting to mitigate the dilution effects of extracranial disease progression on the translation of central nervous system (CNS) control to overall survival, but did not mandate this through systematic restaging. Even so, approximately one-third of patients had extracranial progression, which raises the issue of extracranial death as a competing risk.[7]

Chang et al[8] performed a phase III study in patients who had one to three brain metastases that compared the approach of combination of SRS and WBRT versus SRS alone (MDACC NCT00460395).[8] The primary endpoint of this study was neurocognitive function, as measured by the Hopkins Verbal Learning Test-Revised (HVLT-R).[8] The trial was stopped early after 58 patients were accrued because of a high probability that the SRS-plus-WBRT arm would show a significant decline in learning and memory function (total recall) at 4 months compared with SRS alone. Similar to the previous two studies, there were more CNS recurrences in the group treated with SRS alone; 73% of patients in the SRS-and-WBRT group were free from CNS recurrence at 1 year, compared with 27% of patients who received SRS alone ($p = 0.0003$). In this trial, the WBRT arm was associated with inferior survival, an issue that has become rather controversial but is most likely explained by maldistribution of patients on this small trial relative to the extent of extracranial disease, a factor that would categorically drive mortality.

EXPANDING THE HORIZONS OF STEREOTACTIC RADIOSURGERY

Although SRS typically is offered for patients with four or fewer brain metastases, it is increasingly utilized for patients with five or more lesions. A retrospective study showed that the median overall survival in patients with five or more brain metastases was 7.5 months after treatment with SRS.[9] Interestingly, the number of brain metastases was not a significant predictor of survival, but higher intracranial burden (higher volume of brain metastases within the brain) predicted for poorer outcomes.[10] In a prospective, observational study for one to 10 brain me-

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KEY POINTS

- Selection of local therapy for brain metastases requires a multidisciplinary approach that includes neurosurgery, radiation oncology, medical oncology, and neuro-oncology.
- Treatment with whole-brain radiotherapy (WBRT) after surgery or radiosurgery improves local and distant brain failure but does not improve survival.
- Stereotactic radiosurgery (SRS) increasingly is employed in the management of these metastases in combination with surgery, WBRT, and medical systemic therapies.
- Prospective, randomized trials are needed to define the role and applications of WBRT and SRS.
- Areas of active investigation include techniques (e.g., pharmacologic, hippocampal sparing) to preserve neurocognitive function with radiotherapy.

tastases performed in 23 hospitals in Japan, no difference in overall survival was demonstrated in patients who had two to four brain metastases versus five or more brain metastases when treated with SRS alone.[11] The median overall survival after SRS was 13.9 months in patients who had a single brain metastasis, 10.8 months in patients who had two to four brain metastases, and 10.8 months in patients who had five to 10 brain metastases. This suggests that SRS may be a reasonable approach in selected patients with up to 10 brain metastases, further broadening the horizon of use of SRS in these patients. This also supports the hypothesis that the volume, and not the number, of metastases may be the driver in determining the outcomes in brain metastases.[12] An ongoing prospective trial, NAGKC 12-01, is comparing the neurocognitive outcomes and survival in patients with five or more brain metastases treated either with SRS or WBRT (NCT01731704); this trial will further define the role of SRS in this patient population.

Another active area of interest is utilization of SRS in lieu of WBRT to prevent local recurrence after resection. Resection bed SRS targeting is more complex because of uncertainties about the interpretation of postoperative MRI. Soltys et al[13] showed a 1-year local control rate of 94% with the addition of a 2-mm margin around the defined tumor bed versus 78% when there was no margin.[13] The median overall survival time was 17 months, and 72% of patients were able to avoid WBRT, although intracranial relapse and salvage with other therapies (such as SRS) was required in a substantial proportion of patients. Concerns with this approach include the possibility of leptomeningeal spread secondary to the resection, especially for patients who have breast cancer and those who have posterior fossa disease.[14] The North Central Cancer Treatment Group (NCCTG) study N107C is an ongoing intergroup study of patients who have one to four brain metastases that compares WBRT versus SRS after resection (NCT01372774).

An approach to potentially minimize leptomeningeal spread is to perform neoadjuvant SRS before surgery to sterilize the tumor cells before surgical resection. Neoadjuvant SRS in 47 patients, who were undergoing preoperative SRS with a median dose of 14 Gy (range, 11.8 to 18 Gy), was reported by Asher et al.[15] Surgical resection performed after SRS resulted in control in 86% at 1 year, and only 15% of the patients eventually required WBRT. Significantly, no leptomeningeal failures were observed in this study.

There is no level-1 evidence to support use of SRS in lieu of surgery. More than one randomized effort to answer this question has failed because of poor accrual. In a retrospectively matched series of 75 patients treated by surgery and SRS, a median survival time of 7.5 months with SRS versus 16.4 months in the surgical group was reported.[16] However, the dosing regimen for SRS in this study resulted in the use of lower prescriptions to the tumor margin than would be considered standard according to the widely accepted RTOG dosing schema.[5,17] Auchter et al[18] reported a multi-institutional data set of SRS in 122 highly selected patients who had one resectable brain metastasis. The median survival was 56

weeks in this retrospective series, which was comparable to the results of most surgical series.[18] Schoggl et al[19] performed a retrospective case-control analysis with 133 patients who were treated with either SRS (67 patients) or surgery (66 patients) along with WBRT. There was no difference in median survival (SRS vs. surgery, 12 vs. 9 months; p = 0.19), but the local control rate was superior with SRS.[19] In a retrospective study that compared surgery and SRS for the treatment of a solitary brain metastasis, no significant difference was found in patient survival. However, the difference in the local tumor control rate was significant (100% after SRS vs. 58% after surgery).[20] Muacevic et al[21] compared surgery and WBRT with SRS in patients who had single brain metastases.[21] The approaches— of surgery and WBRT, or of SRS—resulted in similar 1-year survival rates (53% vs. 43%; p = 0.19), 1-year local control rates (75% vs. 83%; p = 0.49), and 1-year neurologic death rates (37% vs. 39%; p = 0.8).

THE ABANDONMENT OF WHOLE-BRAIN RADIOTHERAPY

The randomized studies discussed above demonstrate that postoperative WBRT clearly improves intracranial control of brain metastases, but they also demonstrate that this benefit has not categorically translated into an overall survival benefit. Further, there are concerns regarding the potential for cognitive decline in patients receiving WBRT. More importantly, there are emerging data presented by Sahgal et al[22] showing an overall survival advantage of SRS alone over WBRT (10 vs. 8.2 months) for patients age 50 or younger who have one to four brain metastases, on the basis of a meta-analysis of three phase III studies.[22] Collectively, these factors, as well as the ability to salvage intracranial relapses with further application of SRS (an opportunity afforded in abundance by withholding WBRT), recently have led to the wholesale abandonment of WBRT, with its use reserved largely for patients who have multiple brain metastases and are not deemed favorable SRS candidates.

This approach requires thoughtful scrutiny. The analysis by Sahgal et al[22] was conducted by merging the EORTC 22952-26001, JROSG99-1, and MDACC NCT00460395 data sets. Collectively, these three trials included patients who had one to four brain metastases, who were treated with SRS with or without WBRT, and who had variable entry criteria for each trial and considerable variability in terms of systemic therapies, enrollment eras, SRS dose, follow-up imaging, and re-treatment considerations. Further, the EORTC trial also included patients undergoing resection at physician discretion. A total of 364 patients is available in this collated data set, of whom 51% (185 patients) were treated with SRS alone and only 19% (69 patients) were younger than age 50. The results demonstrate a curious blend of outcomes; for the post hoc–defined subset of these patients younger than age 50, the overall survival was superior with the SRS-alone arm (10 vs. 8.2 months), but the time to distant brain failure was shorter

for patients older than age 55 who were treated with SRS alone (4.5 vs. 6.5 months). The time to local failure was superior with the use of WBRT (7.4 vs. 6.6 months). Crucially, it is important to recognize that the recommendation regarding the survival gain in the younger patient category with SRS alone is based on approximately 35 patients per arm and on a post hoc analysis of a cohort in which the pre-enrollment balance regarding the extent of systemic disease could not be assured, because structured pre-SRS staging—a necessary element for assessing overall survival as an endpoint to avoid systemic burden as a confounder—was not performed.

Therefore, it is reasonable to hypothesize that, in reality, the survival benefit from WBRT is likely limited primarily to patients who do not experience extracranial disease progression. Unless this question is studied in such an enriched cohort, most other studies would likely remain significantly underpowered to demonstrate a survival advantage. In fact, as early as 1998, Pirzkall et al[23] reported on a 236-patient retrospective cohort and found a trend toward improved longer-term survival in favor of SRS plus WBRT (actuarial 1- and 2-year survival rates: 30% and 14% vs. 19% and 8%). More importantly, for patients without extracranial disease, the median survival was impressively (but not significantly) different at 15.4 vs 8.3 months (p = 0.08) in favor of WBRT.[23] More recently, Wang et al[24] retrospectively reviewed a 528-patient database (lung cancer, 257 patients; breast cancer, 102 patients; melanoma, 62 patients; renal cell carcinoma, 40 patients) from Columbia University; patients were treated between 1998 and 2013 with SRS alone (206 patients), with SRS and WBRT (111 patients), with resection followed by SRS (109 patients), or with all three modalities (102 patients). The overall median survival was 16.6 months; for patients who had a single brain metastasis, the median survival times after SRS, SRS plus WBRT, SRS plus resection, and all three modalities were 9.0, 19.1, 25.5, and 25.0 months, respectively. Even for patients who had more than one metastasis, the corresponding median survival times were 8.6, 20.4, 20.7, and 24.5 months, respectively, which demonstrated the survival inferiority of SRS alone as a modality in this cohort. This inferiority associated with the use of SRS alone as a modality was validated in a multivariate analysis.[24]

The data that call the meta-analysis by Sahgal et al[22] most into question, however, come from one of the key sources used within that analysis, JROSG 99-1. At the JASTRO 2014 annual meeting, Aoyama et al (personal communication, March 2015, quoted with permission) presented their own reanalysis of this study, using the now widely accepted disease-specific Graded Prognostic Assessment (ds-GPA), a prognostic stratification tool.[25] Because the ds-GPA relies on molecular variables for stratifying patients who have breast cancer, information that was not collected on JROSG 99-1, these patients could not be adequately categorized and were excluded; 88 (of the 132 total enrolled patients) patients who had non–small cell lung cancer were grouped into favorable (ds-GPA of 2.5 to 4; 47 patients) and unfavorable (ds-GPA of 0.5 to 2; 41 patients) categories. The median survival time was 16.7 versus 10.6 months in favor of the WBRT arm over SRS alone (p = 0.03) for the favorable group, but a similar survival improvement was not observed in the unfavorable group (personal communication, March 2015, quoted with permission). This lends credence to the hypothesis that in patients with a high ds-GPA category, improved brain control translates to a survival advantage because these patients do not die as rapidly from extracranial progression. Therefore, the beneficial effects of improved brain control from WBRT actually affect overall survival. This is quite contrary to the current wisdom of reserving WBRT only for the prognostically least-favorable group of patients. This issue, therefore, remains unresolved.

THE ELEPHANT IN THE ROOM: NEUROCOGNITIVE ISSUES

Diffuse radiographic periventricular white matter changes (leukoencephalopathy) after cranial radiation have been well described and occur at a far higher frequency with WBRT than with SRS.[26] The pathogenesis and clinical relevance of this difference, however, is not well established. In contrast, neurocognitive dysfunction after cranial radiation is multifactorial and is typically mild to moderate in most people; however, this remains one of the most distressing side effects of WBRT and often is the rationale for not utilizing it. However, the clinical results with and without WBRT, in the context of SRS, remain mixed. As mentioned previously, Chang et al[8] demonstrated a decline in HVLT-DR associated with WBRT. Aoyama et al,[6] in contrast, demonstrated that progressive disease has a greater impact than WBRT in terms of cognitive decline, with patients who receive SRS alone experiencing a faster decline in scores of the mini mental status examination.[6,8] The NCCTG, in concert with NRG Oncology, recently has completed accrual to a phase III trial (N0574) comparing SRS versus SRS followed by WBRT for patients who have one to three brain metastases, with built-in early cognitive change as an endpoint. Results are pending.

Mitigation of cognitive dysfunction, therefore, has become an important research direction. The RTOG performed two studies to try to modulate this side effect. In the study RTOG 0614, patients were randomly assigned to receive memantine, an NMDA receptor agonist, versus placebo.[27] The patients in the memantine arm had a significantly longer time to cognitive decline (p = 0.02). The median decline on HVLT-R scale was 0 in the memantine arm compared with −2 in the placebo arm (p = 0.059). Fewer patients treated with memantine had a decline in the Controlled Oral Word Association test at 16 weeks (p = 0.004) or in the Trail-Making test part A at 24 weeks (p = 0.014).

Hippocampal neural stem cell injury from irradiation during WBRT may play a role in memory decline, primarily by shifting the stem cell maturation cycle from neurogenesis to gliogenesis, a phenomenon that is well established in preclin-

ical models.[28,29] In a prospective human study, a strong association with increasing hippocampal radiation dose and neurocognitive dysfunction was demonstrated.[30] Intensity-modulated radiotherapy can be used to conformally avoid the hippocampal neural stem cell compartment during WBRT (HA-WBRT). This hypothesis was tested in a single-arm phase II study of HA-WBRT for brain metastases that used a prespecified comparison with a historic control of patients treated with WBRT without hippocampal avoidance (RTOG 0933).[31] The primary endpoint was change in HVLT-DR measured at 4 months. The historic control (without hippocampal avoidance) resulted in a 30% mean relative loss in HVLT-DR from baseline to 4 months. The actual observed mean relative decline in HVLT-DR from baseline to 4 months was, in fact, only 7.0%, which was significantly lower than the historic control of 30% (p = 0.0003). No decline in quality-of-life scores up to 6 months was

seen.[31] These observations now form the basis of two newer phase III trials, NRG CC 001 and CC 002.

CONCLUSION

The management of brain metastases has evolved over the years from palliation to an era of exciting active research. Local therapies (WBRT, SRS) are important modalities in the management of brain metastases. Areas of active investigation include techniques to preserve neurocognitive function with radiotherapy. The optimal management strategy for these patients involves a multidisciplinary approach that accounts for individual characteristics of both the patient and the tumor. A number of ongoing prospective clinical trials will help further define the role and application of WBRT and SRS in the management of brain metastases.

Disclosures of Potential Conflicts of Interest

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CENTRAL NERVOUS SYSTEM TUMORS

Rare Tumors of the Central Nervous System: More Similar than Different

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Biology and Clinical Management Challenges in Meningioma

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OVERVIEW

Meningiomas are the most frequently occurring intracranial tumors. They are characterized by a broad spectrum of histopathologic appearance. Molecular alterations driving meningioma development, which affect the *NF2* gene, are found in roughly 50% of patients. Rare genetic events in benign meningiomas are mutations in *TRAF7*, *KLF4*, *AKT1*, and *SMO*; all of these mutations are exclusive of *NF2* alterations. Progression to a clinically aggressive meningioma is linked to inactivation of *CDKN2A/B* genes, and a plethora of signaling molecules have been described as activated in meningiomas, which supports the concept of successful clinical use of specific inhibitors. Established treatments include surgical resection with or without radiotherapy delivered in a single fraction, a few large fractions (radiosurgery), or multiple fractions (fractionated radiotherapy). For recurrent and aggressive tumors, inhibitors of the vascular endothelial growth factor (VEGF) pathway, such as vatalinib, bevacizumab, and sunitinib, showed signs of activity in small, uncontrolled studies, and prospective clinical studies will test the efficacy of the tetrahydroisoquinoline trabectedin and of *SMO* and *AKT1* inhibitors.

Meningiomas are tumors that arise from meningeal coverings of the brain and spinal cord. According to current epidemiologic data, they are the most common intracranial tumors, with an incidence of 7.7 per 100,000. Meningiomas are tumors of older populations, with a clear increase in incidence after the age of 65.[1] They preferentially affect women, with a female:male ratio of 3.5:1.[2] Meningiomas in children are exceptionally rare. Risk factors other than age include exposure to ionizing radiation,[3] the presence of diabetes mellitus or arterial hypertension, and, possibly, smoking; the use of mobile phones does not seem associated with an increased tumor risk.[4-6]

CLINICAL PRESENTATION AND RISK FACTORS

Approximately 90% of meningiomas develop from the cranial meninges, although 10% occur in the spinal meninges. The clinical presenting symptoms reflect the anatomic region that is involved and compressed by tumor or peritumoral edema. In many cases, patients with small meningiomas are asymptomatic, and the tumors are found incidentally as a result of imaging for other purposes.

Some patients may present with multiple meningiomas. Among these cases, approximately 1% of multiple occurrences is associated with *NF2*, and 4% of these cases are unrelated to *NF2*.[7] Hereditary meningiomas in adults are highly associated with *NF2* alterations (see below), and 50% to 75% of patients with neurofibromatosis type 2 (NF2) develop me-

ningiomas during their lifetime.[8] Meningioma development in other familial tumor syndromes is uncommon.

PATHOLOGY AND DIFFERENTIAL DIAGNOSES

Meningiomas originate from arachnoidal cap cells, which form the outer layer of the arachnoid mater and the arachnoid villi; the villi are responsible for cerebrospinal fluid (CSF) drainage into the dural sinuses and veins. Arachnoidal cap cells can appear either as a single fibroblast-like cell layer or as epitheloid nests that form several layers. Embryonically, the meninges at the skull base are derived from the mesoderm, and the telencephalic meninges are derived from the neural crest.[9] With age, arachnoidal cap cell clusters become increasingly prominent, forming whorls and psammoma bodies identical to those found in meningiomas. On the basis of cytologic and functional similarities to meningioma cells, arachnoidal cap cells are favored as the most likely cell of origin.[10]

As the neoplastic counterpart of cap cells, meningiomas can have both mesenchymal and epithelial features, reflected by the histopathologic appearance of the most frequent meningioma subtypes (Table 1). Approximately 80% are World Health Organization (WHO) grade 1 meningiomas, which consist mainly of meningothelial, fibrous, or mixed (transitional) tumors. There is a preponderance of specific intracranial sites affected by meningiomas in association with certain histopathologic subtypes. Meningothelial (epithelial) meningiomas are frequently found at the skull base, whereas fi-

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TABLE 1. Meningioma Subtypes, Grading, and Associated Molecular Alterations

Histologic Subtype	WHO Grade	Molecular Alteration*
Meningothelial meningioma	1	NF2
Fibroblastic meningioma	1	NF2
Transitional (mixed) meningioma	l	NF2
Psammomatous meningioma	1	
Angiomatous meningioma	1	
Microcystic meningioma	1	
Secretory meningioma	1	KLF4/TRAF7
Lymphoplasmacyte-rich meningioma	1	
Metaplastic meningioma	1	
Chordoid meningioma	2	
Clear cell meningioma	2	SMARCB1
Atypical meningioma	2	NF2
Brain invasive meningioma	2	
Papillary meningioma	3	
Rhabdoid meningioma	3	
Anaplastic meningioma	3	NF2

*Includes only molecular changes with high frequency and/or association with a specific tumor location.

broblastic meningiomas are more likely to develop at the convexity of the brain.[11,12] If the location is related to the grade of malignancy, the proportion of grade 2 or grade 3 meningiomas at the convexity or with a parasagittal location is much higher than at the skull base.[13] In addition to the three main grade 1 tumor types, other rare variants might be seen, and some of them are associated with specific genetic alterations.

Approximately 20% of meningiomas fall into the group of atypical WHO grade 2 tumors. Interestingly, these tumors have been increasingly recognized in the last few years, mainly as a result of a diagnostic shift from grade 1 to grade 2 meningiomas that is based on a better definition of histopathologic criteria.[14] Atypical meningiomas are characterized by aggressive histologic features, such as increased mitotic activity, nuclear atypia, and necroses. The aggressive biology is reflected by the roughly eight-fold increased risk of recurrence experienced by patients with grade 2 meningio-

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KEY POINTS

- Meningiomas are the most frequent types of intracranial tumors.
- Surgery and radiotherapy are established treatments.
- No standard treatments exist for recurrent/progressive meningiomas.
- Vascular endothelial growth factor pathway inhibitors sunitinib, vatalinib, and bevacizumab showed potential activity in small, uncontrolled studies that require confirmation.

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mas compared with benign WHO grade 1 tumors, and by the considerably increased risk of mortality associated with grade 2 versus grade 1 in with age- and sex-matched controls. Meningiomas with proven brain invasion also are considered grade 2 tumors, and patients with these tumors are prone to an increased risk of tumor recurrence. However, the molecular mechanisms driving brain invasion are not well understood so far. Malignant meningiomas (WHO grade 3) are rare, accounting for only 1% to 2% of all meningiomas, but are associated with a considerable risk of death from disease and an average survival of less than 2 years.[15-17] Although the characteristic histopathologic features of meningiomas are at least focally found in atypical meningiomas, malignant WHO grade 3 meningiomas may completely lack any morphologic hint that points toward a meningeal origin, thus requiring extensive pathologic investigations to confirm the true nature of the tumor.

For differential diagnoses, meningiomas can present with a wide spectrum of histopathologic patterns, and coexistence of various morphologic features within one tumor may occur. Using immunohistochemistry, meningiomas usually express epithelial membrane antigen (EMA) and vimentin. Cytokeratins are usually not expressed, which helps to rule out metastatic carcinoma. Exceptions include secretory meningiomas and some anaplastic meningiomas. Highly vascularized meningiomas must be separated from hemangiopericytoma and solitary fibrous tumor (SFT). There typically is diffuse CD34 positivity in SFT. Extensive staining for CD99 and B-cell lymphoma 2 is common to both SFT and hemangiopericytoma, but it is missing in meningiomas. In contrast, EMA expression is much more typical of meningioma.[10]

MOLECULAR GENETIC ALTERATIONS IN MENINGIOMAS

The first genetic alteration described was the loss of chromosome 22, and chromosome 22 alterations are still the most frequent findings in meningiomas. Subsequently, a gene on chromosome 22 responsible for the hereditary tumor syndrome NF2 was identified.[18,19] Although bilateral vestibular schwannomas are the hallmark of the disorder, the majority of patients with NF2 develop multiple meningiomas, which suggests a role for the NF2 gene in meningioma development.[20] Indeed, allelic losses of chromosome 22, including the NF2 region, occur in more than 50% of sporadic meningiomas.[21-24] In meningiomas with allelic losses (loss of heterozygosity [LOH]) at the NF2 locus, point mutations in the remaining allele can be found in sporadic meningiomas, which suggests complete gene inactivation.[25,26] Merlin, the gene product of NF2, has significant sequence homology to members of the ezrin/radixin/moesin (ERM) family of proteins, which link various cell-adhesion receptors to the cortical actin cytoskeleton.[27] The frequency of NF2 inactivation is roughly equal among different WHO grades, which suggests that NF2 loss is an initiating rather than progression-associated alteration.[16,28-30] With variant histology, differences in the frequency of NF2 alterations have been reported.

Fibroblastic, transitional, and psammomatous have higher frequencies of *NF2* alterations than meningothelial or secretory meningiomas.[28,31-33] Accordingly, patients with non-*NF2* familial multiple meningiomas are more likely to develop meningothelial tumors.[34] An association between the *NF2* gene and location has also been reported, and tumors of the convexity are more likely than anterior cranial-based tumors to harbor *NF2* alterations.[11] In contrast, patients with neurofibromatosis type 1 (NF1) only rarely present with meningiomas,[35] and *NF1* gene mutations are absent in anaplastic meningiomas, which suggests that *NF1* alterations are not involved in meningioma development and/or progression.[30]

Based on the clearly established role of *NF2*, it could be demonstrated that *NF2* inactivation in leptomeningeal cells of conditional *NF2* knockout mice (*NF2*^*flox/flox*) by Cre recombinase injection induces meningiomas.[36] Most of these mouse tumors recapitulate the meningothelial, fibroblastic, or transitional subtype of human meningiomas and are characterized by reduced merlin expression. The knowledge concerning the mechanisms driving the development of the main histopathologic subtypes among grade 1 meningiomas has been expanded recently by generating a mouse model with inactivation of meningeal *NF2* by using the prostaglandin D2 synthase (PGDS) gene promoter. PGDS is a specific marker of arachnoidal cells.[37] *NF2* inactivation in PDGS-positive meningeal progenitor cells resulted in both meningothelial and fibroblastic meningiomas.[38] Of note, *NF2* inactivation in mice led to meningioma development only during a critical prenatal and perinatal time frame.

On the basis of recent whole genome-sequencing approaches, few other recurrent genetic alterations have been identified recently in benign meningiomas. In 2013, four genes altered in a small fraction of meningiomas—*TRAF7*, *KLF4*, *AKT1*, and *SMO*—were identified.[29,39,40] Probably the most important new mutation identified is related to the v-akt murine thymoma viral oncogene homolog 1 gene (*AKT1*), with a hotspot mutation (p.Glu17Lys) named *AKT1*^E17K. This somatic mutation occurs in breast, ovarian, and colorectal cancers.[41,42] In meningioma, this mutation was found nearly exclusively in 7% to 12% of WHO grade 1 meningiomas but was (exceptionally) rare in grade 2 and was absent in grade 3 tumors.[39,40] The *AKT1*^E17K mutation was found predominantly in the meningothelial/transitional subtypes, and tumors that harbored the *AKT1*^E17K mutation were *NF2* wild type. Another gene found mutated in grade 1 meningiomas was the receptor-associated factor 7 gene (*TRAF7*).[39] *TRAF7* is located on chromosome 16p13 and encodes a proapoptotic protein that interacts with multiple signaling pathways. *TRAF7* mutations are mutually exclusive of *NF2* mutations and occur in approximately 24% of meningiomas.[39] They are present in 93% to 100% of secretory meningiomas.[43] In addition, meningiomas with *TRAF7* mutations are almost always characterized by the mutation K409Q in the gene for the transcription factor Kruppel-like factor 4 (*KLF4*). *KLF4*, located on chromosome 9q, is involved in transcriptional activation and repression.[44] The combined

TRAF7/KLF4 mutation characterizes secretory meningiomas[39,43] and provides a molecular marker for this grade 1 subtype. Meningiomas with *TRAF7/KLF4* mutations are predominantly located at the medial/lateral skull base.

Another non–*NF2*-associated mutation of skull base meningiomas affects the Smoothened gene, *SMO*. *SMO* mutations occur in 4% to 5% of grade 1 meningiomas and are restricted to the medial anterior skull base near the midline. *SMO* mutations are exclusive of *NF2* and of *AKT1* or *TRAF7/KLF4*.[29,39]

Although all of these mutations are mutually exclusive of *NF2* alterations, other genetic alterations occur in association with chromosome 22 in meningiomas. One gene located on chromosome is *SMARCB1*, and alterations are frequently found in *SMARCB1* in pediatric malignant rhabdoid tumors. Screening a large group of sporadic meningiomas revealed that *SMARCB1* mutations occur with low frequency and might be cooperating with *NF2* mutations, because tumors showing both *SMACRB1* and *NF2* mutations were reported.[45,46] *SMARCB1*-mutated meningiomas are preferentially found at the falx cerebri.[47]

In families with multiple spinal meningiomas and without *NF2* mutations, a loss-of-function mutation in the *SMARCE1* gene was recently identified.[48] *SMARCE1* is located on chromosome 17q21 and encodes for a 57-kDa subunit of the SWI/SNF complex, which is involved in the regulation of chromatin structure by nucleosome remodeling. The mutation occurs selectively in spinal meningiomas with histologic features of clear cell meningioma, so it providing a potential molecular hallmark for this rare meningioma subtype.

The merlin protein belongs to the protein 4.1 family, with members linking the membrane protein to the cytoskeleton. One gene of the protein 4.1 family relevant for meningioma biology is *DAL1*. Reduced expression of the *DAL1* gene product protein 4.1B was found in approximately 60% of meningiomas regardless of histologic grade, which suggests that protein 4.1B loss is another early event in meningioma pathogenesis.[49,50] Nearly all tumors with *DAL1* LOH have simultaneous *NF2* LOH.[51] Mice lacking *DAL1* do not develop tumors,[52] which suggests that *DAL1* alterations are early progression–associated steps. In patients with multiple meningiomas, *DAL1* mutations were found in both tumor and paired blood samples, which suggests substantial differences between patients with sporadic single and multiple meningioma with respect to *DAL1*.[34]

MALIGNANT PROGRESSION IN MENINGIOMA

Meningiomas are generally thought to progress from low-grade to high-grade tumors. Histologically, progression from grade 1 to grade 2 can be confirmed in 17% to 38% and from grade 1/2 to grade 3 in 54% to 70%.[53,54] At the cytogenetic level, a stepwise acquisition of chromosomal gains and losses during meningioma progression has been proven.

Losses of 1p, 6q, 10q, 14q, and 18q, as well as gains of 1q, 9q, 12q, 15q, 17q, and 20q have been proposed as important events in meningioma progression and recurrence,[29,55-59]

and 1p and 14q loss especially are associated with meningioma progression.[60-62] Interestingly, 1p loss commonly is found in tumors located at the convexity but is rare in skull base or spinal meningiomas.[13] Moreover, 1p loss is associated with faster meningioma recurrence.[63] Losses of 6q, 9p, 13, and 14 are found exclusively in highly proliferating meningiomas.[64] Radiation-induced aggressive meningiomas show cytogenetic aberrations on chromosome 1p, 6q, and 22.[65]

Few specific genes associated with chromosomal alterations have been identified. Besides *NF2*, the tissue inhibitor of metalloproteinase 3 gene (*TIMP3*), location on 22q12, is another gene associated with meningioma progression . Hypermethylation of the *TIMP3* promoter occurs in 17% of benign, 22% of atypical, and 67% of anaplastic meningiomas and is associated with allelic loss on 22q12.[66] The TIMP3 protein inhibits matrix metalloproteinases, which suggests that epigenetic inactivation of *TIMP3* by promoter hypermethylation might favor aggressive invasive tumor growth. *TIMP3* has additional tumor suppressor activity, and in vitro overexpression of *TIMP3* reduces tumor growth and induces apoptosis.[67] However, *TIMP3* hypermethylation does not seem associated with tumor recurrence or overall survival.[63]

Alterations on 9p21 have been found to represent losses of the tumor suppressor genes *CDKN2A* ($p16^{INK4a}$), $p14^{ARF}$, and *CDKN2B* ($p15^{INK4b}$).[30,68] In anaplastic grade 3 meningiomas, deletions of *CDKN2A*/*CDKN2B* are associated with poorer survival.[69] In mouse models, deletion of *CDKN2A*, together with *NF2* inactivation, results in increased meningioma frequency and the development of grade 2 or 3 meningiomas, which proves that loss of *CDKN2A* and *CDKN2B* is a feature for aggressive meningioma development.[70]

Amplification of the S6 kinase gene region on chromosome 17q23 is present in malignant meningiomas,[71,72] which suggests that mammalian target of rapamycin (mTOR) signaling pathway inhibition might be a therapeutic target.[73] The 14q32 region has been implicated in meningioma progression because of the maternally expressed gene 3 (*MEG3*), which has antiproliferative activity in meningiomas. Aggressive meningiomas show allelic losses, promoter hypermethylation, and reduced expression of *MEG3* compared with normal arachnoidal cells.[74,75] The important role of chromosome 14q loss was supported by findings that showed *NDRG2* as a gene commonly inactivated in meningioma progression. *NDRG2* is downregulated in anaplastic meningiomas and in a small subset of lower-grade meningiomas and atypical meningiomas with aggressive clinical behavior. The reduced expression of *NDRG2* is associated with promoter hypermethylation.[76,77]

MOLECULAR FACTORS AFFECTING MENINGIOMA PROGNOSIS

The histologic tumor grading is one of the strongest factors influencing tumor recurrence and overall prognosis.[17] A high MIB-1 labeling index is associated with poor prognosis.[78] Losses of 1p and 14q have a poor prognostic implication.[60-63,79-81] Patients who have tumors greater than 50

mm and a combined loss of 1p and 14q represent a subgroup at high risk for early relapse.[82] Relapse-free survival is negatively associated with male sex, presence of brain edema, intraventricular and anterior cranial base tumor location, age younger than 55, and tumor size larger than 50 mm.[83]

MOLECULAR SIGNALING PATHWAYS

Molecular signaling pathways, including those involved in mitogenic signal transduction, have been studied intensively in meningiomas. Nearly all of the growth factor receptors/kinases known to be involved in tumor growth (epidermal growth factor receptor [EGFR], platelet-derived growth factor receptor [PDGFR] beta, vascular endothelial growth factor receptor [VEGFR], insulin-like growth factor receptor [IGFR]) have been expressed in meningiomas.[84-87] Mitogenic signals of EGFR and PDGFR are mediated by the Ras-Raf-Mek-MAPK pathway. Indeed, these pathways are activated in meningiomas.[88,89] The phosphoinositide 3-kinase–AKT/protein kinase B p70 signaling pathway is another important mediator of growth-favoring signals in meningiomas.[73,89,90] The mTOR signaling pathway is of relevance for both *NF2* mutant meningiomas and for meningiomas with other mechanisms of mTOR pathway activation, such as *S6K* gene amplification.[71,72] Merlin (*NF2*) is a negative regulator of the mTOR complex 1 (mTORC1) kinase complex, and constitutive activation of mTORC1 signaling is present in meningioma cells from patients with NF2.[91,92] Other signaling pathways activated in meningiomas include the phospholipase A2-arachadonic acid-cyclooxygenase pathway[93,94] and the PLC-gamma1-PKC pathway.[89,95] The transforming growth factor-beta (TGF-beta)-SMAD signaling pathway represents an inhibitory mechanism, and TGF-beta, and the TGF-beta receptor, are expressed in meningiomas.[96-98] All of these activated signaling pathways represent potential therapeutic targets.

MANAGEMENT OF MENINGIOMAS

The overall management approach for newly diagnosed meningiomas is usually dependent on a number of factors including the patient's age, comorbidities, and clinical symptoms as well as the tumor location (proximity to critical structures or regions of brain), size, and mass effect. For patients who are symptomatic as a result of the mass effect from the tumor, surgery is typically recommended. For other patients, discussion with the patient and interdisciplinary discussion of all management options, including observation, surgical resection, and radiotherapy (including radiosurgery and fractionated radiotherapy) are considered.

OBSERVATION

For patients who have asymptomatic meningiomas that are not in close proximity to critical structures, an observational approach may be considered. Most meningiomas are low

grade and have annual growth rates of 1 to 3 mm per year.[99] If an observational approach is taken, close follow-up with serial imaging and clinical neurologic assessment is required to avoid overlooking the development of symptoms that suggest more rapid tumor growth. If tumor growth is documented or if clinical symptoms develop or progress, discussion about treatment should be revisited.

SURGERY

The usual initial treatment is surgical excision of the tumor and its dural base, particularly for tumors located on the outer brain surface and surgically easily accessible. After gross total resection (i.e., complete excision of the tumor and its dural attachments) of a benign meningioma, the risk of tumor recurrences are 5%, 10%, and 30% at 5, 10, and 15 years, respectively.[100] The extent of surgery is reported by Simpson grade. Sughrue et al[101] reported that, for patients who have grade 1 meningioma, the extent of resection impacts the risk of recurrence and progression-free survival. After Simpson grade 1, 2, 3, and 4 resections, the respective 5-year progression-free survival rates were 95%, 85%, 88%, and 81%.[101]

Not all meningiomas can be totally resected without an unacceptable risk of postoperative neurologic deficits. For skull-based meningiomas, a particular surgical risk is cranial nerve palsy.[102-104] Newer microsurgical and endoscopic techniques in combination with advances in neuroimaging have improved the outcomes of surgical resection of meningiomas.[105,106] Finally, there has been a move toward optimizing functional preservation by utilizing a combination of the currently available surgical and radiotherapy techniques personalized to the patient and particular clinical situation over achieving radical resections that results in functional loss.

RADIOTHERAPY

The role of radiotherapy in the management of meningiomas depends on patient factors, such as their comorbidities and preference, and on tumor factors, including tumor size, resectability, and—particularly— grade. Radiotherapy also is usually recommended for recurrent meningiomas after initial surgical resection, either as monotherapy or as adjuvant therapy after reresection.[107]

In general, radiotherapy is recommended after surgical resection of malignant (WHO grade 3) meningiomas because of the considerably better 5-year progression-free survival seen with surgery followed by adjuvant radiotherapy (80%) compared with surgery alone (15%).[108] Radiotherapy was shown to shrink any remaining tumor burden in addition to preventing tumor recurrence.[109,110]

For atypical (WHO grade 2) meningiomas, the optimal timing of radiotherapy is less clear, particularly after a complete resection. Retrospective studies have demonstrated that early adjuvant radiotherapy for nonbenign meningiomas improves progression-free survival, but the majority of these studies have evaluated grade 2 and 3 meningiomas together, and the benefit may reflect selection bias of higher risk cases to receive adjuvant radiotherapy versus those that did not receive radiotherapy postoperatively.[108,111-113] As the goals of treatment shift toward optimizing functional outcome and minimizing treatment-related toxicity, close observation is typically preferred after a gross total resection of a grade 2 meningioma. After an incomplete resection or at the time of tumor recurrence, radiotherapy options, including potential radiosurgery or fractionated radiotherapy, are offered, depending on the volume and location of the tumor.[114]

For WHO grade 1 meningiomas, there is even greater controversy about the optimal management, because there are a greater number of management options, including observation, radiosurgery alone, fractionated radiotherapy alone, surgical resection alone, or a combination of surgery with postoperative radiosurgery or fractionated radiotherapy. After surgical resection, there is controversy about early postoperative radiotherapy versus delayed radiotherapy at the time of tumor recurrence. Data support the improved local control of early adjuvant radiotherapy compared with surgery, particularly after partial resection.[115] In contrast, a delay in radiotherapy until tumor recurrence can help spare radiotherapy and its associated toxicities in a proportion of patients who do not experience tumor recurrence.[116]

Radiosurgery

Radiosurgery can be delivered with a variety of devices, including the Gamma Knife, Cyberknife, and a linear accelerator (LINAC). A single fraction to a marginal dose of 10 to 15 Gy is usually given.[117,118] Because treatment of a larger target volume results in greater treatment-related toxicity, radiosurgery typically is offered to tumors that are smaller volume and not in very close proximity to critical structures, such as the optic chiasm.[119] In a multicenter study of 254 patients treated up front for petroclival meningioma with radiosurgery (140 patients) or with radiosurgery after surgery (144 patients), the actuarial progression-free survival rates were 93% and 84% at 5 and 10 years, respectively.[120] Similar tumor control, with actuarial 5- and 10-year progression-free survival rates of 95% and 92%, respectively, has been reported for sellar and parasellar meningiomas treated with a single-fraction radiosurgery treatment to a median prescription dose of 13 Gy (range, 5 to 30 Gy).[121]

Fractionated Radiotherapy

Fractionated radiotherapy is often delivered with stereotactic radiotherapy (SRT) or image-guided radiotherapy approaches to optimize the precision of radiotherapy delivery in combination with intensity-modulated radiotherapy techniques to improve the dose shaping around complex targets in close vicinity to critical normal structures. For benign meningiomas, fractionated radiotherapy is offered for large volume tumors or those in very close proximity to critical structures, such as the optic chiasm. The volume that is targeted for benign tumors is typically the enhancing tumor, with a minimal margin for set-up error. The radiation dose

generally ranges between 50 and 56 Gy and is delivered in fractions of 1.8 to 2.0 Gy. After a median follow-up of 43 months (range, 2 to 144 months), Soldà et al[122] reported similar local control rates for fractionated radiotherapy as reported for radiosurgery; 5- and 10- year local control rates were 93% and 86%, respectively. For higher-grade meningiomas, there is greater concern for brain invasion and, therefore, the target volume includes an additional margin for microscopic spread, typically 1 to 2 cm. Because of the more aggressive biology, higher doses of radiation are generally used for higher-grade meningiomas, ranging between 60 66 Gy.[108,112,123]

Proton Therapy

Proton therapy provides the potential benefit of a more conformal dose distribution that can cover the tumor with a higher dose of radiation while minimizing entry, exit, and overall integral radiation dose. At the present time, the ability to generate a highly conformal proton radiotherapy plan is user and center dependent. Using standard fraction sizes of 1.8 Gy and total doses of 50.4 to 66.6 Gy for grade 1 meningiomas and doses of 54.0 to 72.0 Gy for grade 2 meningiomas, the results from Loma Linda show a 5-year actuarial control rate of 96%, with better control for grade 1 meningiomas (99% at 5 years) compared with grade 2 meningiomas (50% at 5 years). No associations with local control and total dose were seen in this retrospective review, but increased optic neuropathy was seen with higher doses delivered to tumors in close proximity to the optic apparatus.[124] Gudjonsson et al[125] reported their outcomes of stereotactic hypofractionated proton radiotherapy using doses between 14 Gy in three fractions to 24 Gy in four fractions. They reported no signs of tumor progression after 36 months of follow-up of 19 patients with partially resected grade 1 (15 patients) or unresectable (4 patients) meningiomas. However, two patients developed clinical signs and radiologic evidence of a radiation reaction with this hypofractionated approach.[125]

SYSTEMIC THERAPIES

Systemic therapies are usually considered in patients who experience progression after exhaustion of all local treatment options (surgical resection, radiotherapy) and in the rare cases of metastatic meningiomas. Unfortunately, the lack of adequately designed and powered clinical trials on systemic therapeutics in meningiomas prohibits treatment planning on a high level of evidence. On the basis of documented low response rates and progression-free survival times, a number of drugs, including hydroxyurea, interferon alfa, octreotide analogs (sandostatin, pasireotide), mifepristone, megestrol acetate, imatinib, erlotinib, and gefitinib are not considered beneficial agents.[126] However, some agents have shown promising signs of efficacy in preclinical investigations and small clinical studies that may translate into clinically relevant activity if confirmed in larger, prospective clinical trials.

Evidence from several studies indicates that antiangiogenic agents may have some therapeutic value in meningiomas. Indeed, pathologic neoangiogenesis and upregulation of angiogenic pathways, such as the vascular endothelial growth factor axis, repeatedly have been shown in meningiomas, thus providing a pathobiologic rationale for such agents.[86,127,128] Some case reports and small retrospective patient series have shown relatively high 6-month progression-free survival rates for recurrent/progressive meningiomas treated with the VEGF-A-binding monoclonal antibody bevacizumab.[129-134] Further data on the efficacy of bevacizumab is awaited from ongoing single-arm phase II trials enrolling patients with recurrent, progressive WHO grade 1, 2, and 3 meningiomas (NCT01125046, NCT00972335). So far, no unexpected toxicities of bevacizumab were seen in this patient population. Of note, bevacizumab has a marked antiedematous effect that may lead to clinical improvements and reduced corticosteroid need.[135]

Vatalinib (PTK787/ZK22584), a tyrosine kinase inhibitor of VEGFR1 to VEGFR3, was tested in a series of 24 patients with meningiomas of all grades. Toxicities were manageable and included fatigue (60%), hypertension (24%), and elevated transaminases. Favorable 6-month progression-free survival rates of 64.3% and 37.5% were seen in grade 2 and 3 tumors, respectively.[136]

A recent publication reported the results of a prospective, multicenter, phase II trial that enrolled patients with surgery and radiation-refractory recurrent grade 2 to 3 meningioma in a primary cohort and patients with WHO grade 1 meningioma, hemangiopericytoma, or hemangioblastoma in an exploratory cohort.[126] Patients were treated with the tyrosine kinase inhibitor sunitinib, which targets VEGF, platelet-derived growth factor (PDGF), c-KIT, FLT, macrophage colony-stimulating factor (CSF-1R), and RET. Thirty-six patients were enrolled in the primary cohort and 13 patients in the exploratory cohort. In the primary cohort, the 6-month progression-free survival rate was 42%, which met the primary endpoint. Toxicity, however, was substantial with one grade 5 intratumoral hemorrhage, two grade 3 and one grade 4 CNS/intratumoral hemorrhages, one grade 3 and one grade 4 thrombotic microangiopathy, and one grade 3 gastrointestinal perforation. Interestingly, tumoral VEGFR2 expression correlated with favorable outcome, thus introducing a potential biomarker for response to sunitinib therapy.

Several upcoming clinical trials have been designed according to preclinical data and may introduce novel medical options for the therapy of meningiomas. The EORTC-1320 trial will evaluate in a randomized fashion the effect of trabectedin on progression-free survival versus local standard-of-care therapy. Trabectedin is a tetrahydroisoquinoline originally isolated from the sea squirt *Ecteinascidia turbinate* and is approved for the treatment of advanced sarcoma and recurrent ovarian cancer. Trabectedin binds to the minor groove of the DNA, induces apoptosis in tumor cells as well as depletion of tumor-associated macrophages, and has antiangiogenic properties.[137,138] Another multicentric clinical trial will prospectively evaluate the efficacy of *SMO* and *AKT1* inhibitors in mutation-bearing meningiomas.

Disclosures of Potential Conflicts of Interest

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DEVELOPMENTAL THERAPEUTICS AND TRANSLATIONAL RESEARCH

Antibody-Drug Conjugates: New Horizons to Maximize Efficacy and Minimize Toxicity

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What Can We Learn about Antibody-Drug Conjugates from the T-DM1 Experience?

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OVERVIEW

Antibody conjugates are a diverse class of therapeutics that consist of a cytotoxic agent linked covalently to an antibody or antibody fragment directed toward a specific cell surface target expressed by tumor cells. The notion that antibodies directed toward targets on the surface of malignant cells could be used for drug delivery is not new. The history of antibody conjugates has been marked by hurdles identified and overcome. Early conjugates used mouse antibodies, drugs that either were not sufficiently potent, were immunogenic (proteins), or were too toxic, and linkers that were not sufficiently stable in circulation. Four main avenues have been explored using antibodies to target cytotoxic agents to malignant cells: antibody-protein toxin (or antibody fragment−protein toxin fusion) conjugates, antibody-chelated radionuclide conjugates, antibody-small molecule conjugates, and antibody-enzyme conjugates administered along with small molecule prodrugs that require metabolism by the conjugated enzyme to release the activated species. Technology is continuing to evolve regarding the protein and small molecule components, and it is likely that single chemical entities soon will be the norm for antibody-drug conjugates. Only antibody-radionuclide conjugates and antibody-drug conjugates have reached the regulatory approval stage, and there are more than 40 antibody conjugates in clinical trials. The time may have come for this technology to become a major contributor to improving treatment for patients with cancer.

The challenges posed by the development of therapeutic antibody-drug conjugates (ADCs) are formidable. Over the past 30 years, many cell surface proteins that have selective aberrant expression on malignant cells or are aberrantly highly expressed on the surface of malignant cells have been identified. In many cases, specific antibodies that bind tightly to malignant cell surface proteins were developed. However, these antibodies often were not active antitumor agents. ADCs provide an opportunity to make use of antibodies that are specific to cell surface proteins.[1] Successful ADCs have improved tumor specificity and potency compared with traditional drugs.[2,3] Heterogeneity of antibody target expression on the tumor surface, and expression of the antigen by normal tissues, can limit the effectiveness of ADCs. For some hematologic malignancies, antigen expression is specific and homogeneous.

Early ADCs were composed of tumor-specific murine monoclonal antibodies covalently linked to anticancer drugs, such as doxorubicin, vinblastine, and methotrexate. These early conjugates were evaluated in human clinical trials but had limited success because of immunogenicity, lack of potency, and insufficient selectivity for tumor versus normal tissue. The lessons learned from these early explorations led to improvements in all aspects of antibody conjugate therapeutics and, hence, to renewed interest in ADC technology.[4] Immunogenicity was overcome by replacing murine antibodies with humanized or fully human antibodies. Potency was improved by using drugs that were 100- to 1,000-fold more potent than previously used drugs. Selectivity was addressed by performing more careful target and antibody selection. As a result of such improvements, gemtuzumab ozogamicin (Mylotarg; Pfizer, New York, NY) was granted accelerated U.S. Food and Drug Administration (FDA) approval for the treatment of acute myelogenous leukemia in 2000, becoming the first commercially available ADC. However, gemtuzumab ozogamicin was withdrawn from the market in 2010 because, in postmarketing follow-up clinical trials, it failed to meet the prospective efficacy targets. Two ADCs, trastuzumab emtansine (T-DM1, Kadcyla; Genentech/Roche, South San Francisco, CA) and brentuximab vedotin (SGN-35; Adcetris, Seattle Genetics, Seattle, WA; Millennium/Takeda, Boston, MA), reached FDA approval in 2014 and 2011, respectively, for treatment of metastatic breast cancer and refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma, respectively. More than 40 ADCs are in clinical trials (Table 1).

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TARGETS AND ANTIBODIES

In selecting cell surface protein targets, whether on malignant cells, on malignant disease–associated cells (e.g., tumor endothelial cells), or in the tumor microenvironment, it is important that the antigen expression is abundant on the target cells or in the tumor region and is very limited on all other cells and normal tissues.[5-9] The patient whose tumor expresses high levels of the target antigen is most likely to benefit from treatment. ADCs are targeted, potent cytotoxic agents. Most of the proteins being targeted with antibody conjugates are normal proteins, as opposed to mutant proteins; therefore, some antigen expression on normal cells is possible and even likely. Technologies for antibody discovery, development, and engineering are well established. Phage display libraries and humanized mice can produce fully human antibodies, and mouse antibody humanization can result in highly specific nonimmunogenic antibodies (Fig. 1). In most cases, the most appropriate antibody for ADC therapeutics requires that the antibody-target complex internalize into the target cells where the drug is released.

DRUGS

The drugs most widely conjugated to form ADCs target tubulin or DNA and are uniformly highly potent cytotoxic agents with 50% inhibitory concentration (IC_{50}) values in the picomolar range in cell culture.

Though ADCs are among the most tumor-selective anticancer therapeutics developed to date, only a small fraction of the drug reaches the intracellular target. The maytansinoids and dolastatin analogs target tubulin, and both suppress microtubule dynamics.[10] The duocarmycins and calicheamicins target the minor groove of DNA. The amatoxin analogs inhibit RNA polymerase II and III, and SN-38 targets toposiosmerase I, which results in DNA double-strand breaks.[11] These molecules have in

KEY POINTS

- Most antibody-drug conjugate (ADC) targets are cell surface proteins that are much more abundant on tumor cells than on normal cells/tissues.
- ADCs selectively deliver targeted chemotherapy and could be important components of combination treatment regimens.
- ADCs are being targeted to solid tumors and to hematologic malignances.
- The three components of ADCs, antibody, linker, and drug, must be stable in circulation for days or weeks.
- T-DM1 and brentuximab vedotin are the first two ADCs to gain regulatory approval for HER2-positive metastatic breast cancer and Hodgkin lymphoma, respectively. Patient selection and understanding about the toxicity profiles of these agents are critical for integration of ADCs into inpatient care.

TABLE 1. ADCs in Clinical Development

Conjugate Name	Target	Company
Gemtuzumab ozogamicin, Mylotarg	CD33	Pfizer
Trastuzumab emtansine, T-DM1	HER2	Roche-Genentech
Brentuximab vedotin, Adcetris	CD30	Seattle Genetics-Takeda
Inotuzumab ozogamicin, CMC-544	CD22	Pfizer
CDX-011, Glembatumumab vedotin	GPNMB	Celldex Therapeutics
SAR3419, huB4-DM4	CD19	Sanofi
Lorvotuzumab mertansine, IMGN901	CD56 (NCAM)	ImmunoGen
Vorsetuzumab mafodotin; SGN-75	CD70	Seattle Genetics
PSMA ADC	PSMA	Progenics
Pinatuzumab vedotin; RG7593	CD22	Roche
Polatuzumab vedotin; RG7596	CD79b	Roche
RG7450	STEAP1	Roche
AGS-5ME	AGS-5 (SLC44A4)	Astellas
AGS-22M6E	Nectin-4	Astellas
SAR566658, huDS6-DM4	CA6 (Muc1)	Sanofi
Indatuximab ravtansine; BT-062	CD138 (syndecan-1)	Biotest
Milatuzumab-DOX	CD74	Immunomedics
BAY 94-9343	Mesothelin	Bayer Pharma
IMGN529	CD37	ImmunoGen
IMGN853	FOLR1	ImmunoGen
Labetuzumab-SN-38; IMMU-130	CEACAM5	Immunomedics
MLN0264	Guanylyl cyclase	Millennium-Takeda
IMMU-132	Trop-2	Immunomedics
AMG-595	EGFR vIII	Amgen
AMG-172	CD70	Amgen
AGS-15E	SLITRK6	Astellas
AGS-16C3F	ENPP3	Astellas
RG-7458	MUC16	Roche
GSK2857916	BCMA	GSK
IMMU-132	Trop-2	Immunomedics
HuMax-TF	Tissue factor	Genmab
IMGN-242	CanAg	ImmunoGen
IMGN-289	EGFR	ImmunoGen
IMGN-388	Alpha v-integrin	ImmunGen
IMGN-633	CD33	ImmunoGen/Sanofi
MEDI-547	EphA2	MedImmune
MLN-0264	GCC	Takeda
MLN-2704	PSMA	Takeda
PF-06263507	5T4	Pfizer
SAR-566658	huDS6 (Mucin 1)	Sanofi
SC16LD6.5	SC-16	Stem CentRx
SGN-19A	CD19	Seattle Genetics
SGN-CD33A	CD33	Seattle Genetics
SGN-LIV1A	LIV1 (ZIP6)	Seattle Genetics

Abbreviations: ADC, antibody-drug conjugate; DOX, doxorubicin; EGFR, epidermal growth factor receptor.

FIGURE 1. Antibody-Drug Conjugate Schematic
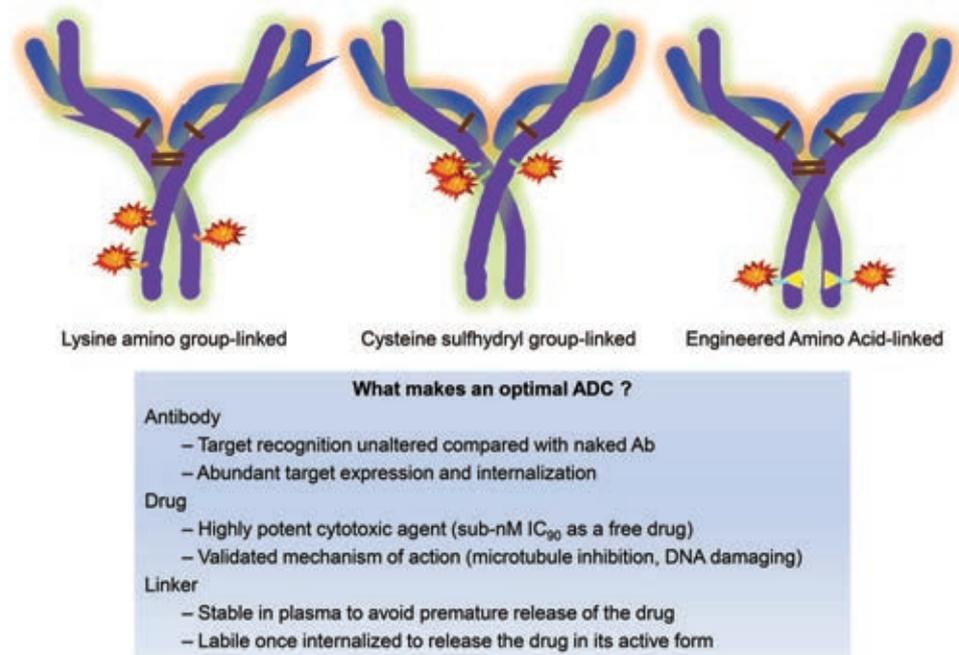
The drug is linked through the epsilon amino groups of lysine, through the intrastrand sulfhydryl linkages, and through genetically engineered unnatural amino acids to provide specific binding sites and, thus, a single chemical species.

common an extreme potency and a lack of tumor selectivity, which limits the use of the parent compounds. Dolastatin 10, the parent molecule of the auristatins, was explored in clinical trials in the 1990s, but exploration was terminated in 1995 when the drug failed in a phase II trial in patients with prostate cancer.[12] The maytansinoids are exquisitely potent cytotoxic agents. Maytansine was assessed in early clinical trials in the early 1980s. The phase II clinical trials were disappointing, with very little evidence of response.[13] Duocarmycins are antibiotics that alkylate DNA in the A-T–rich regions of the double-helix minor groove. Several duocarmycins were evaluated in clinical trials, and dose-limiting toxicities occurred at doses too low to achieve antitumor activity.[14,15] Calicheamicins bind in the DNA minor grove and induce double-strand breaks, but they have narrow therapeutic indices and serious late toxicities.[16,17] SN-38, the active metabolite of irinotecan, is poorly bioavailable and has a narrow therapeutic index.[18] Amatoxins, cytotoxic cyclopeptides that target RNA polymerases, are produced by poison mushrooms. Normal tissue toxicities of the amantins precluded their clinical exploration.[19]

ADCs are an effective method to increase the therapeutic index of these highly potent cytotoxic agents. The drugs used in ADCs must have sufficient water solubility and prolonged stability in aqueous formulations and in plasma, and they must have a functional group that is suitable for conjugation with a linker and that must not be readily susceptible to lysosomal enzyme degradation. Consistent with the potent nature of the drug, ADCs are often scheduled like cytotoxic chemotherapy in clinical regimens, with dosing once every 3 weeks.[20-22]

LINKERS

Linkers are short spacers that covalently couple the drug to the antibody protein and must be stable in circulation (Fig. 1). Inside the cell, most linkers are labile; however, some are stable, requiring degradation of the antibody and linker to release the cytotoxic agent.[23,24] Many linkers react with lysine side chains throughout the antibody or with the sulfhydryls in the hinge regions of the antibody. Linkers in clinical use include acid-labile hydrazone linkers that are degraded under the low pH conditions found in lysosomes. Disulfide-based linkers are selectively cleaved in the cytosol in the reductive intracellular milieu. Noncleavable thioether linkers release the drug after degradation of the antibody in the lysosome, and peptide linkers, such as citrulline-valine, are degraded by lysosomal proteases in cells. Linkers using L- and D-alanine and beta-glucuronide linkers are being explored. Linkers with polyethylene glycol spacers have been developed to increase the solubility of the conjugate.[25,26]

Linkers can influence the circulating half-life and safety of conjugates by minimizing the release of the drug molecule in circulation and optimizing the delivery of the conjugate to the target tissue. Often, during drug development, investigators will test several linkers in safety and efficacy assays to select the best candidate conjugate.

ADCs

Drug-loading stoichiometry and molecular homogeneity are important determinants of the safety and efficacy of antibody conjugates (Fig. 1). The goal is to develop ADCs that are sin-

gle chemical species or nearly single chemical species. Under-conjugated antibody decreases ADC potency, and highly-conjugated antibody markedly decreases circulating half-life and impairs binding to the target protein, thus decreasing ADC potency and efficacy.[27] For most ADCs, linkage of three to four drug molecules per antibody molecule is optimal to maintain the circulating half-life to near that of the naked antibody, preserving antibody binding to the target protein, and delivering a lethal number of drug molecules to the target cell. Several site-specific conjugation approaches are being explored to achieve ADCs that are single chemical species. Antibodies with site-specific incorporation of non-native amino acid linker sites can be efficiently produced.[28]

FROM THEORY TO PRACTICE: T-DM1 CASE STUDY

Mechanisms of ADC action for T-DM1 include all of the effects of trastuzumab plus the effects of the conjugated maytansine derivative. T-DM1 binds HER2, and the HER2/T-DM1 complex undergoes internalization, followed by lysosomal degradation. This process results in the intracellular release of DM1-containing catabolites that bind to tubulin

and prevent microtubule polymerization as well as suppress microtubule dynamic instability. T-DM1 also has been shown to retain the mechanisms of action of trastuzumab, including disruption of the HER3/phosphoinositide 3-kinase (PI3K)/AKT signaling pathway and Fcγ receptor–mediated engagement of immune effector cells, which leads to antibody-dependent cellular cytotoxicity (Fig. 2).[29]

INTEGRATION OF T-DM1 IN CLINICAL PRACTICE

The experience with trastuzumab over the past 2 decades has facilitated the rapid integration of T-DM1 for the treatment of HER2-positive metastatic breast cancer (HER2+ MBC). HER2 testing must be performed at the time of diagnosis or recurrence for all invasive breast cancers. HER2 positivity is defined as protein expression using immunohistochemistry (score, 3+), or as *HER2* gene amplification using fluorescence in situ hybridization.[30] Unless there is a contraindication, trastuzumab-based chemotherapy is recommended for the treatment of HER2+ breast cancer in the adjuvant, neoadjuvant, and metastatic settings.[31] Pertuzumab has been shown to be effective as part of neoadjuvant taxane/trastuzumab-based

FIGURE 2. Structure of T-DM1 and Mechanisms of Action
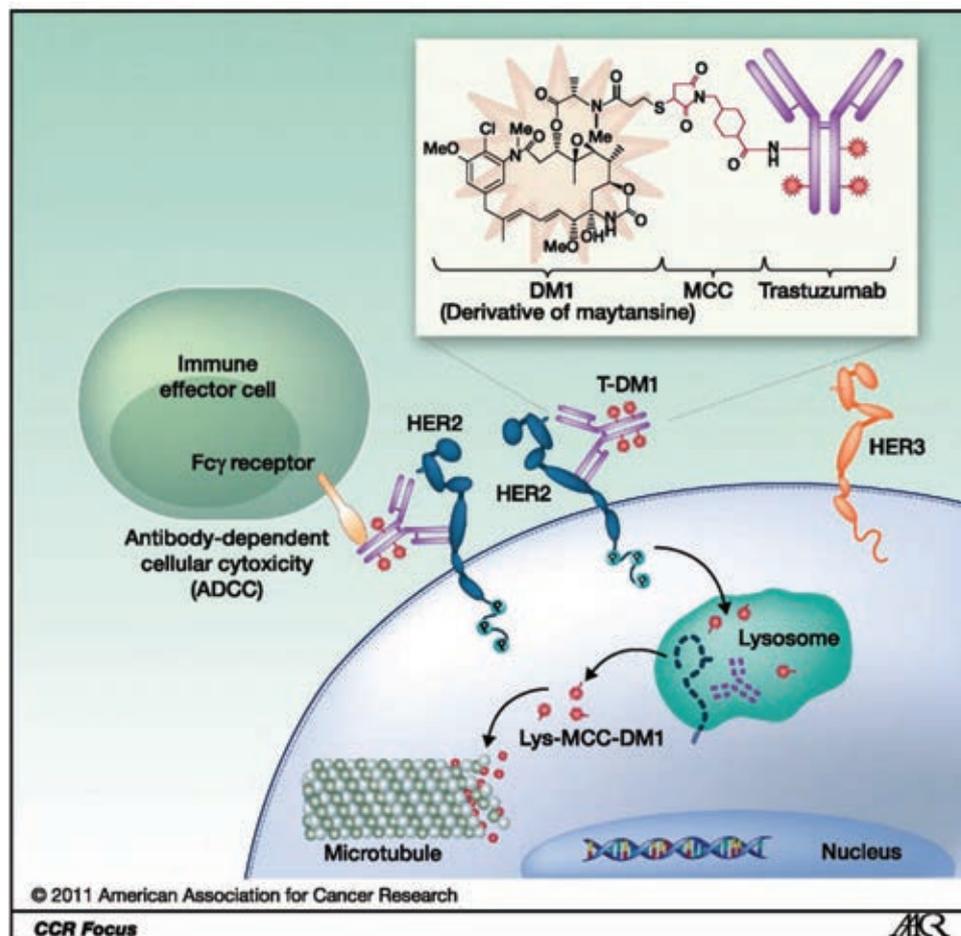
T-DM1 binds HER2; the complex is internalized and degraded in lysosomes, releasing DM1. T-DM1 retains the mechanisms of action of trastuzumab, including antibody-dependent cellular cytotoxicity and HER pathway signaling disruption.

regimens[32] and as first-line therapy for HER2+ MBC.[33-35] Lapatinib is approved in combination with capecitabine for patients whose tumors have progressed on trastuzumab-based therapy.[36] A combination of lapatinib and trastuzumab has been shown to improve overall survival rates in patients with HER2+ MBC who have experienced progression after multiple regimens.[37] For details regarding the management of HER2+ MBC, please refer to the American Society of Clinical Oncology (ASCO) clinical practice guideline.[38] On the basis of the results of the EMILIA randomized trial described below,[39] the FDA-approved T-DM1 (Kadcyla, Genentech, South San Francisco) in February 2013 for the treatment of patients with HER2-overexpressing MBC who have received prior treatment with trastuzumab and a taxane.

T-DM1: PATIENT SELECTION

All clinical trials of T-DM1 used HER2 protein overexpression and/or *HER2* gene amplification as one of the key inclusion criteria. As with all other HER2-directed therapies, T-DM1 appears to be effective only against HER2+ tumors. Ongoing clinical trials are evaluating the role of T-DM1 in other solid tumors that either overexpress HER2 protein and/or amplify the *HER2* oncogene (e.g., gastric cancer) or carry *HER2* mutations (e.g., NCI-MATCH trial).

Phase I and phase II trials of T-DM1 showed objective responses in patients with HER2+ MBC with an acceptable toxicity profile, leading to the design of pivotal phase III, randomized trial (EMILIA). In this study, patients with HER2-positive MBC were randomly assigned to T-DM1 or to capecitabine in combination with lapatinib. One of the key inclusion criteria was prior trastuzumab- and taxane-based chemotherapy. In this study, T-DM1 therapy improved response rate, time to progression, and overall survival rate compared with the combination of capecitabine and lapatinib.[39] In addition, T-DM1 was better tolerated than capecitabine plus lapatinib.

The TH3RESA global trial was launched to determine the effectiveness of T-DM1 in heavily pretreated patients (beyond second line) who had HER2+ MBC. In this study, more than 600 patients with progressive MBC who had been previously treated with trastuzumab and lapatinib were randomly assigned to either T-DM1 or to a standard treatment of the physician's choice. The final results showed a 3-month improvement in the median progression-free survival time in the T-DM1 group. Response rates were improved in the T-DM1 group (31% in T-DM1 vs. 9% in control group).[40] There was a suggestion of an improved overall survival rate for patients treated with T-DM1, although the data are not mature. Importantly, T-DM1 was better tolerated than other standard chemotherapies. On the basis of these results, T-DM1 is now considered a new standard treatment after multiple lines of therapy for patients who have HER2+ MBC.

After obtaining regulatory approval for T-DM1 when progression develops after trastuzumab treatment, the next logical step was to evaluate the efficacy of this novel ADC in the first-line setting. The MARIANNE trial recruited more than 1,000 patients with HER2+ MBC who had not received any chemotherapy in the metastatic setting. In this study, patients were randomly assigned to receive a taxane/trastuzumab, T-DM1, or T-DM1 plus pertuzumab (Perjeta; Genentech/Roche, South San Francisco, CA). However, this trial did not include a comparator arm with taxane, trastuzumab, and pertuzumab, which is the standard first-line therapy for HER2+ MBC.[33] Though detailed data have not yet been shared, the sponsor recently announced that the MARIANNE trial did not reach its primary endpoint.[41]

On the basis of the encouraging results reported in patients with metastatic disease, there is great interest in testing the efficacy of T-DM1 for early-stage breast cancer. An ongoing, single-arm, phase II trial (NCT01196052) is evaluating the efficacy of T-DM1 in the adjuvant or neoadjuvant setting. After completion of an anthracycline-based adjuvant/neoadjuvant chemotherapy regimen (doxorubicin/cyclophosphamide [AC] or 5-fluorouracil/epirubicin/cyclophosphamide [FEC]), 153 patients will be treated with T-DM1 instead of the conventional taxane/trastuzumab combination for 17 cycles. In the ATEMPT trial (NCT01853748), 500 patients with stage I breast cancer will be randomly assigned to T-DM1 versus paclitaxel plus trastuzumab. In the KAITLIN trial (NCT01966471), 2,500 patients will be randomly assigned after adjuvant AC/FEC to either a taxane, trastuzumab plus pertuzumab, or T-DM1 plus pertuzumab. A randomized, phase III trial (KATHERINE; NCT01772472) will evaluate the efficacy of T-DM1 in patients who have residual disease after neoadjuvant, trastuzumab-containing regimens. In this study, patients are randomly assigned to continuation of trastuzumab (standard treatment) or to T-DM1. This study has a planned enrollment of more than 1,400 patients. The KRISTINE trial will examine the combination of docetaxel, carboplatin, trastuzumab, and pertuzumab (one of the FDA-approved neoadjuvant pertuzumab-containing regimens) versus T-DM1 plus pertuzumab. All of these trials will provide key data to integrate T-DM1 in the treatment of HER2+ early-stage breast cancer.

MANAGEMENT OF T-DM1 OFF-TARGET TOXICITIES

It is important to understand common off-target toxicities caused by T-DM1 and to manage them appropriately (Table 2).

Thrombocytopenia was reported in phase I and phase II clinical trials of T-DM1. In the EMILIA trial, the incidence of grade 3 or worse thrombocytopenia was 12.9% in the T-DM1–treated group and was 0.2% in the lapatinib/capecitabine group (overall incidence, 28% and 2.5%, respectively). The mechanism of T-DM1–induced thrombocytopenia is puzzling, because platelets do not overexpress HER2. Recent data indicate that thrombocytopenia may be mediated in part by DM1-induced impairment of megakaryocytic differentiation, with a less-pronounced effect on mature megakaryocytes.[42] For most patients receiving T-DM1, thrombocytopenia is asymptomatic and can be monitored without any changes in treatment. Platelet counts should be monitored before ini-

TABLE 2. Management of T-DM1 Off-Target Toxicity

Toxicity	Management
IRRs	T-DM1 treatment should be interrupted in patients with severe IRRs and permanently discontinued in the event of a life-threatening IRR. Patients should be closely monitored for IRRs, especially during the first infusion.
Thrombocytopenia	Platelet counts should be monitored prior to initiation of T-DM1 and prior to each T-DM1 dose. Dose modifications should be instituted as appropriate.
Hemorrhage	Consider additional monitoring when concomitant use of anticoagulants or antiplatelet therapy is medically necessary.
Hepatotoxicity	Reduce the dose of T-DM1 if serum transaminases or total bilirubin are elevated. Discontinue the drug if abnormal liver function tests persist.
Left Ventricular Dysfunction	Hold T-DM1 if LVEF drops below normal (usually 50%) or is a >15% decrease from a prior level. Discontinue the drug if LVEF does not recover to normal levels.
Pneumonitis	Discontinue the drug.
Neurotoxicity	Monitor for signs or symptoms of neurotoxicity. T-DM1 should be temporarily discontinued in patients experiencing grade 3 or 4 peripheral neuropathy until it resolves to grade ≤2.

Adapted from the Kadcyla package insert.[58]
Abbreviations: T-DM1, trastuzumab emtansine; IRR, infusion-related reaction; LVEF, left ventricular ejection fraction.

tiation of T-DM1 and before each T-DM1 dose. Dose modifications should be instituted as appropriate.

T-DM1 can cause serious hepatotoxicity, including liver failure and death. Serum transaminases and bilirubin must be monitored before initiation of T-DM1 treatment and before each T-DM1 dose. If serum transaminases or total bilirubin are increased, the dose of T-DM1 should be reduced or discontinued.

T-DM1 administration may lead to reductions in left ventricular ejection fraction (LVEF). All patients should undergo evaluation of LVEF before and during treatment with T-DM1. If a patient develops a clinically meaningful decrease in left ventricular function, the treatment should be held.

T-DM1 FOR THE TREATMENT OF BRAIN METASTASES

Involvement of the central nervous system remains one of the major challenges for patients with HER2+ MBC.[43] ASCO has recently published a clinical practice guideline for patients with HER2+ breast cancer and brain metastases.[44] Despite all efforts, prognoses remains poor for these patients, and novel approaches are needed. Anecdotal reports suggest that T-DM1 can be effective for the treatment of HER2+ brain metastases.[45,46] A retrospective analysis of the EMILIA trial showed a low incidence of brain metastasis in patients treated with T-DM1 (1.8%) and in patients treated with lapatinib and capecitabine (0.6%). A total of 95 patients had controlled brain metastases at study entry. Only 2% of patients treated with T-DM1 and 1.6% of patients assigned to lapatinib

and capecitabine developed progressive disease in the central nervous system during the study. Although progression-free survival was similar for all patients with brain metastasis at baseline, the median overall survival was significantly longer in patients treated with T-DM1 compared with lapatinib and capecitabine (26.8 vs. 12.9 months; hazard ratio [HR], 0.382; p = 0.0081).[47] These data provide a rationale to study the safety and efficacy of T-DM1 in combination with stereotactic radiosurgery and other radiation therapy modalities.

NOVEL ADCs AND RATIONAL COMBINATIONS

The ability of ADCs to deliver chemotherapy neatly to the tumor not only offers the potential for greater efficacy and reduced toxicity as monotherapy but also expands the potential of combination regimens. In the case of T-DM1, virtually any agent that one would consider adding to a trastuzumab/chemotherapy backbone could be considered for addition to T-DM1. Conceptually, one could group the potential combinations into several broad categories including (1) anti-HER2 agents, (2) cytotoxics, (3) inhibitors of parallel growth factor pathways, and (4) inhibitors of downstream signaling molecules. Though a large number of clinical trials are ongoing, few trials have reported results thus far.

In vitro, T-DM1 and pertuzumab act synergistically; xenograft models confirm enhanced tumor inhibition with the combination compared with either agent alone.[48] T-DM1 and pertuzumab can be combined at full doses with no unexpected toxicities. In previously treated patients, T-DM1 plus pertuzumab had similar activity (objective response rate, 33%; progression-free survival, 5.5 months) to that observed with single-agent T-DM1 (objective response rate, 26% to 35%; progression-free survival, 4.6 to 6.9 months)[22,49,50] and with pertuzumab plus trastuzumab (objective response rate, 24%; progression-free survival, 5.5 months).[51] In previously untreated patients, the objective response rate was 57% and the median progression-free survival time was 7.7 months (95% confidence interval [CI], 3.71 to 15.87 months).[52] The order of treatment may be important; in preclinical models, pretreatment with pertuzumab appeared to blunt the efficacy of T-DM1.[53]

At first thought, the combination of T-DM1 and an unconjugated cytotoxic seems an anathema—why add the toxicity of another chemotherapy agent to one designed partly to minimize toxicity? In patients with low-risk disease, that argument may be persuasive, but the goal of increased efficacy predominates in patients with aggressive, high-risk disease. Ongoing trials explore the potential to combine T-DM1 with a variety of chemotherapy agents, including paclitaxel, docetaxel, and capecitabine, among others. Alternatively, T-DM1 has been substituted for the taxane/trastuzumab portion of adjuvant therapy for high-risk patients in the ongoing KAITLIN trial.

HER2+, hormone receptor–positive (HR+) breast cancer is a distinct subtype associated with a good prognosis but a lower response to standard chemotherapy plus anti-HER2 agents. Concurrent blockade of the HER2 and estrogen receptor pathways has been a successful strategy, increasing

objective response rates and progression-free survival in patients with advanced disease.[54,55] The ADAPT HER2+/HR+ trial compared T-DM1 monotherapy to T-DM1 plus endocrine therapy (premenopausal patients: tamoxifen; postmenopausal patients: aromatase inhibitor or trastuzumab plus endocrine therapy as neoadjuvant therapy). The treatment with T-DM1 plus endocrine therapy resulted in a greater median fractional decrease in proliferation (Ki67) after 3 weeks of therapy (40% in the T-DM1/endocrine therapy arm vs. 14% and 25% in the T-DM1 monotherapy and trastuzumab/endocrine therapy arms, respectively).[56]

T-DM1 is an ideal candidate to combine with agents that have been difficult to combine with chemotherapy because of overlapping toxicities. Ongoing trials combine T-DM1 with a variety of downstream signaling inhibitors and other molecular pathways, including inhibitors of heat shock proteins, cyclin-dependent kinases, PI3K/AKT, and mammalian target of rapamycin (mTOR).

Importantly, T-DM1 may be considered a prototype and is almost certainly just the first ADC for the treatment of HER2-expressing breast cancer. The potential to use HER2 as a molecular address also may increase the proportion of patients who could benefit from HER2-targeted agents. For example, SYD985 is an HER2-targeting ADC that combines trastuzumab and a duocarmycin payload with a cleavable linker. In cell lines with low HER2 expression (i.e., HER2 2+ and 1+), SYD985 had both in vitro and in vivo activity.[57] If confirmed in the clinic, this could extend the target population of patients with breast and gastric cancers who may respond to this treatment modality to include those with fluorescence in situ–negative or immunohistochemistry-negative HER2 2+ and 1+ disease.

Disclosures of Potential Conflicts of Interest

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DEVELOPMENTAL THERAPEUTICS AND TRANSLATIONAL RESEARCH

Enrolling Patients in Early-Phase Clinical Trials: An Ethical Dilemma

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OVERVIEW

The overall aging of the population has resulted in a marked increase in the number of older patients with cancer. These patients have specific needs that are different from those of the younger population. Cancer clinical trials have included an inadequate number of older patients, resulting in lack of meaningful data to make evidence-based decisions for this population. As a result, clinicians have to extrapolate data from younger and healthier patients. There are a number of reasons for this under-representation, including a design and implementation structure for clinical trials that does not meet the needs of this vulnerable population. Issues that need to be addressed include alterations in eligibility criteria to make them less restrictive by accounting for multiple comorbidities and prior malignancy and endpoints specific for older patients, such as quality of life, changes in function, and maintenance of independence. Other issues specific to the older population include alterations in dose-limiting toxicity, measures of treatment-related toxicity, and polypharmacy. Phase I trials can be appropriate for older patients but need to be tailored to their needs. Some form of geriatric assessment needs to be included to help with eligibility, assessment, and stratification. For future clinical trials to be truly meaningful they need to appropriately assess and incorporate the needs of the majority of the cancer population.

The demographic shift and the resultant increase in the number of older patients with cancer, which was predicted by the founders of geriatric oncology (Dr. B.J. Kennedy, Dr. Rosemary Yancik, and others), has now arrived. It has long been recognized that the most significant risk factor for the development of cancer is aging. Cancer and its treatment can affect the overall life expectancy, as well as the active life expectancy and function, of older individuals. The traditional study approach to cancer, with its focus on younger, healthier patients, has resulted in a lack of high-quality data to adequately guide care for older patients. In 1983, Dr. Yancik organized a symposium sponsored by the National Cancer Institute and the National Institute on Aging and published a monograph, "Perspectives on Prevention and Treatment of Cancer in the Elderly," highlighting the importance of research in cancer and aging.[1] In the 1988 American Society of Clinical Oncology (ASCO) Presidential Address, Dr. Kennedy encouraged the study of aging and cancer.[2] He stated, "Our society need not ration how we will treat our disadvantaged members, but should continue to seek those preventive and positive measures that can shorten our later period of morbidity. A very major cancer load will persist well into the 21st century, even if the attempts at prevention are eventually a total success. There is a developing knowledge on aging. Care of the older person needs to be part of medical education and oncology education. Research will help attain a desirable quality of life with aging and a reduced morbidity."

The goals set forth by Drs. Yancik and Kennedy are yet to be fully achieved; however, many strides have been made toward that end. There has been increased recognition of the importance of the relationship between aging and cancer, as well as an increase in evidence-based research to guide the care of older adults with cancer. In addition, this research is being performed by a growing number of investigators at institutions across the nation, as well as internationally. The International Society of Geriatric Oncology, founded in the year 2000, fosters the mission of developing health professionals in the field of geriatric oncology to optimize treatment of older adults with cancer, through education, clinical practice, and research. The Society's publication, the *Journal of Geriatric Oncology*, is the first journal devoted solely to the field. The Cancer in the Elderly Committee of the Cancer and Leukemia Group B (now the Alliance for Clinical Trials in Oncology) has supported furthering research in geriatric oncology through clinical trials and secondary data analyses. The Cancer and Aging Research Group has developed an instrument to predict chemotherapy toxicity, initiated and supported trials to validate this methodology in different clinical settings, and, most importantly, mentored junior investigators in geriatric oncology. The Gynecologic Oncology Group Elderly Taskforce is supporting the first prospective trial in older women with ovarian cancer and planning further studies in other diseases and modalities. The American Society of Clinical Oncology has also fostered a number of initiatives in geriatric oncology. These

include a Geriatric Oncology Issue Exploration Team, educational materials including ASCO University, sessions at the Annual Meeting including a Geriatric Oncology track, the BJ Kennedy Award for Excellence in Geriatric Oncology, and a Geriatric Oncology component of the Cancer Education Committee.

Older patients have long been under-represented in clinical trials.[3,4] There are many reasons for this, including fear of toxicity, restrictive trial eligibility, and ageism, which includes physician barriers.[5-8] When older patients do participate, they are usually a disproportionately small representation of the patients and their data are under-reported.[9] The Institute of Medicine has issued a report describing the crisis in cancer care for an aging population.[10]

TRIALS SPECIFIC FOR OLDER PATIENTS

Older patients have often been undertreated.[11] In addition, because of the lack of objective data they have been subject to increased toxicity and poor outcomes. Clinical trial eligibility criteria have typically excluded these patients and been unable to meet their needs. Clinicians need objective, age-specific data to make appropriate treatment decisions for these vulnerable patients. The current accrual methods have been inadequate to accrue adequate numbers of older patients into studies. The need for such clinical trials was recognized in 1980 when Begg et al evaluated the studies from the Eastern Cooperative Oncology Group.[12] They showed that the patients in clinical trials did not experience excessive toxicity, compliance was good, and efficacy was equivalent. In 1983, Dr. Yancik organized a symposium sponsored by the National Cancer Institute and the National Institute on Aging and published a monograph, "Perspectives on Prevention and Treatment of Cancer in the Elderly," highlighting the importance of research in cancer and aging.[1] The participants noted a number of pervasive issues, including discrepancies between physiologic and calendar age and changes in the age structure of the nation's population. They recommended analyses of existing databases, prospective clinical trials, epidemiologic and longitudinal studies, pharmacokinetics and drug sensitivity trials, and quality-of-life issues. These recommendations are still relevant. In his ASCO Presidential Address of 1988 and Journal of Clinical Oncology editorial of 1991,[2,13] BJ Kennedy discussed the need to emphasize study of older patients and included physician education as a key factor. In 1994, Trimble et al demonstrated the discrepancy between the incidence of certain cancers and the under-representation of older patients.[14] In 1999, Hutchins et al reviewed participation of Southwest Oncology Group trials and found similar results.[3] Analysis of National Cancer Institute (NCI)-sponsored clinical trials also revealed a need to increase participation of older patients.[15] Despite this, in a subsequent review of cancer drug registration studies, under-representation of older people was again noted.[4] Even 8 years later, a follow-up analysis did not show any substantial improvement.[16] The clinical trial development process has been inadequate to meet the needs of the older population and there is a need to develop a new process and new thoughts on this issue.[17] Trials specific for older patients can incorporate functional and cognitive assessment instruments to help assess the patients. They can also include age-specific pharmacokinetic analyses, evaluation of polypharmacy, and other geriatric syndromes, which would not be possible in studies not specific for this population. Issues regarding barriers to trials and study design are summarized in Sidebars 1 and 2. Following is a discussion of problems related to clinical trial design and possible alternatives.

ELIGIBILITY ISSUES

Restrictive eligibility issues are an important reason why older patients are not accrued to clinical trials. Standard performance status measurements such as Karnofsky Performance Status or Eastern Cooperative Oncology Group (ECOG) are inadequate to define function in older patients.[18] Populations need to be defined more specifically to encompass the broad range of older patients (i.e., frail, vulnerable, or well). This can best be determined by some form of geriatric assessment, which could help in defining the patient population, aid in stratification, and improve analysis of the results.[19,20] The typical end-organ requirements for eligibility need to be made more flexible. For example, renal function requirements can be relaxed when the drug being studied

KEY POINTS

- Aging of the general population will result in a large increase in the number of older patients with cancer.
- Older patients with cancer are under-represented in clinical trials.
- There are a number of barriers that prevent older patients from participating in clinical trials.
- Current clinical trial design is inadequate to appropriately assess the value of newer therapies.
- Components of clinical trials such as eligibility, endpoints, survivorship, and dose-limiting toxicity need to be re-evaluated.

SIDEBAR 1. Barriers to Participation in Clinical Trials[17]

- Physician recommendation
- Social: transportation, caregiver issues
- Financial: not all study drugs covered, multiple visits not covered
- Trial design
  - Restrictive eligibility
  - "Excessive" visits
- Perception of aggressive therapy
- Limited expectation of benefit from patient or family

does not have a renal mechanism of clearance. Limiting office visits and testing will facilitate compliance by allowing patients with limited social supports to participate and minimizing caregiver burden. Many older patients have had previous cancer treatment; therefore, prohibition of a prior diagnosis of malignancy and treatment needs to be reconsidered. For diseases in which survival is relatively short, such as metastatic pancreatic cancer, treatment with localized radiation 5 or 10 years earlier for a localized disease is not relevant. Less restrictive eligibly criteria will allow a broader range of patients to participate in trials. These carefully assessed and monitored patients will yield data that will be applicable to the general population of older patients and will provide a degree of safety in terms of dosing and supportive care. It is fair to state that the doses obtained from phase I trials may not be broadly applied to the geriatric population without further exploration in that population, as we currently do in pediatric populations. A phase I dose should be studied in older patients with varying degrees of function impairment and comorbidity.

ENDPOINTS OF CLINICAL TRIALS

The traditional endpoint of survival may not be appropriate for the older patient and particular care must be must be taken when overall survival is a study endpoint. A number of studies determined that cause of death might differ in older versus younger patient populations. In lymphoma trials, deaths attributed to tumor or treatment-related toxicity were similar for patients older than and younger than 60. The observed differences in survival rate—22% of patients greater than or equal to 60 years of age but only 2% of patients less than 60 years—were instead associated with other causes of death not obviously related to the lymphoma or its therapy. The inclusion of older patients in clinical trials may decrease the overall survival secondary to deaths from ap-

parently unrelated causes.[21,22] Patients with early-stage breast cancer and comorbidity had a 4-fold higher rate of all-cause mortality compared with patients who had no comorbid conditions.[23] This phenomenon is particularly important in cancers that can have a relatively indolent course. In prostate cancer studies, it has been shown that competing causes of death are substantive contributors to mortality.[24,25] Progression-free survival, time without symptoms, measuring treatment-free intervals, or maintenance of independence (or prevention of dependency) may be more meaningful endpoints.

QUALITY OF LIFE IN CLINICAL TRIALS

Patient quality of life is affected by a number of factors related to the cancer and treatment, as well as its interaction with other diseases. Assessment of quality of life is an important endpoint in clinical trials for older adults; however, the traditional view of quality of life may be broadened in an older patient population. For example, the compression of morbidity and disability to maximize the preservation of "active" life expectancy is also a potential quality of life endpoint, particularly in a palliative care setting.[26,27] There are many parallels between geriatric assessment and quality of life assessment in that both are multidimensional and broad. They share many dimensions and focus on issues that are important to older people, particularly the ability to function fully in social roles and participate in daily activities. Quality of life studies have been performed as a predictive marker in non–small lung cancer and have been analyzed in the context of the effect of therapy.[28-30]

FUNCTION AND CLINICAL BENEFIT

Response rate is one of the standard endpoints of phase II studies, whereas survival and disease-free survival are endpoints of phase III studies. Assessment of clinical benefit has become an important endpoint, especially in the management of metastatic disease, and some agents, including gemcitabine for pancreatic cancer[31] and mitoxantrone for prostate cancer,[32,33] have been approved for use because of demonstrated clinical benefits. In the older population, impaired functional status is a risk factor for cancer treatment toxicity and overall survival. Longitudinal changes in functional status are a potential endpoint of clinical trials. This was explored in a clinical investigation of infectious syndromes in older people in which function was used as a risk factor for infectious syndromes as well as an outcome measure.[34] In older individuals with limited life expectancies, improvement in survival may be difficult to demonstrate and clinical benefits may become paramount. In addition to improvement in pain and other symptoms, the benefits of chemotherapy may include prevention of functional dependence and functional deterioration. As this is one of the most common complications of diseases in older individuals, it is surprising that it has not been more commonly explored as

an outcome of cancer treatment. Chemotherapy might not only affect functional status in metastatic incurable cancer, but might also result in changes of functional status in patients whose cancer may be curable, such as patients with breast or colorectal cancer receiving adjuvant chemotherapy and patients with lymphoma.

SURVIVORSHIP

Although not usually part of standard clinical trial design, the issues of survivorship in older survivors of cancer need to be explored.[35-37] As a result of increased utilization of screening and earlier detection of common cancers (i.e., breast, colorectal, and prostate), coupled with incremental improvements in cancer treatment and supportive care, the number of cancer survivors in the United States has increased from approximately 3 million in 1970 to almost 14 million in 2014. Patients age 70 and older account for 46% of all survivors.[38] Survivorship has become a separate, but related, discipline of oncology that requires both expertise and the infrastructure to provide optimal care for cancer survivors. Cancer survivors have unique problems. Pre-existing comorbid issues are often compounded by the residual toxicity of cancer treatment and the possibility of late adverse effects. There are also emotional issues regarding survivorship. The Institute of Medicine has issued recommendations regarding cancer survivorship programs and a number of centers of excellence have been developed to evaluate different survivorship clinical models. These are focusing on many different areas, including behavioral interventions, nutritional interventions, cancer screening, studies of morbidity, physical activity, sexual function, and fatigue.[39-41]

DOSE-LIMITING TOXICITY

Schedule changes may alter the toxicity profile of chemotherapy in an older population. For example, weekly paclitaxel versus paclitaxel and bolus 5-fluorouracil every 3 weeks versus infusional 5-fluorouracil may show differences in toxicity. The commonly used toxicity criteria may not be adequate to assess adverse events in older patients. Neuropathy assessment should include evaluation of functional decline or falls. The reports of studies should be age-specific. Most trials only report grade 3 or 4 toxicity, even though grade 2 toxicity often has clinical relevance. Reporting the full spectrum of toxicity for a clinical trial will help clinicians make treatment decisions. Studies of new agents in predetermined stages of aging (i.e., frail or vulnerable) or in patients with specific common comorbidities or functional impairments would be invaluable. Common Terminology Criteria for Adverse Events (CTCAE) version 4 does incorporate functionality in the grading and could be applied to geriatric patients.

PHASE I STUDIES

Only a limited number of phase I trials have involved older patients, despite the fact that the heterogeneity of this population limits the applicability of results from phase I studies performed in fit, younger patients.[42] Traditionally, during the phase I investigation, acute toxicities are identified and the potential duration and reversibility of the toxicities are defined. Selecting appropriate patients to accurately evaluate toxicity in a phase I clinical investigation is extremely important. Typically, patients included in phase I trials have a good performance status and normal organ function. As a result, entry criteria often exclude older patients from dose-finding trials. However, studies in the older person could be defined differently from what has been done historically. For example, after a phase I dose is determined, older patients with varying degrees of functional impairment or comorbidities can be treated to determine whether the dose is appropriate. ASCO has published a position paper on the importance of phase I studies with suggestions to enhance accrual. They mention the critical role that Medicare has in supporting these trials and by inference, increasing the participation of older patients. Although the position paper specifically cites issues regarding pediatric patients, there is no specificity with respect to older people.[43]

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The Global Conduct of Cancer Clinical Trials: Challenges and Opportunities

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OVERVIEW

The nature of clinical research has changed substantially over the last 2 decades, evolving from being centered almost exclusively in developed countries to a more global scenario that is increasingly involving less developed regions of the world. Pharmaceutical companies and some academic cooperative groups have been conducting challenging, large pivotal registration studies with multinational participation. The much more needed globalization of academic research demands particular attention and represents a worthwhile subject for a more profound discussion. The requirement of large sample sizes and the potential for fast recruitment leading to a speedy completion of clinical studies are probably the most important factors that have fueled globalization of studies. Reduced operational costs and the ability to expedite the regulatory approval of drugs in various countries or regions are also important drivers. Globalization of research should be seen as having a much wider effect in the societies involved, in particular, when we consider public health, economic, social, and ethical implications. Most importantly, the process of expanding the network of clinical research sites also fosters the integration and the development of closer relationships among investigators at a global level. We consider this an essential element that should remain a prominent element in the discussion. In this article, we address the underlying reasons for globalization and we highlight some of the scientific and ethical concerns arising as a consequence. Finally, some strategies to address and mitigate the challenges of conducting multinational clinical research are proposed.

Globalization can be defined as the integration of economies, industries, markets, cultures, and policy-making processes around the world.[1] Even though the concept is not new, the current wave of globalization has been heavily driven and influenced by fantastic and unprecedented advances in the information technology that will likely have a long lasting effect in the process. Even though globalization is frequently approached with a focus in economy, the concept has been increasingly broadened to include a diverse range of areas such as culture, media and technology, socioculture, and the political arena, among others. Proponents of globalization argue that the ultimate result of this international interaction should be economic development and improvement of the standards of living.

Until not so long ago, drug development and cancer clinical research were conducted almost exclusively in wealthy developed regions of the world. However, over the last 2 or 3 decades, clinical trials have been progressively incorporated in a challenging globalization process. As such, the conduct of trials in a global scale represents a major aspect to be taken into account when analyzing the future development of the area. The globalization of clinical trials, as well as multinational and multi-institutional research collaboration, represents a scenario that requires permanent and concentrated efforts by all involved if we are to achieve the fundamental objective of generating the appropriate answers to the health problems we face around the world.

Large pharmaceutical companies have been conducting large pivotal registration studies increasingly with multinational participation, and much has been discussed on the globalization of clinical research addressing the subject from the pharmaceutical industry perspective. However, the much more needed globalization of academic research is at least as challenging, demands particular attention, and represents a worthwhile subject for a more profound discussion as well.

The requirement of large sample sizes and the potential for fast recruitment leading to a speedy completion of clinical studies are probably the most important factors that have fueled globalization of studies, particularly of large registration phase III trials. Other factors may include the reduced operational costs and the ability to expedite the regulatory approval of drugs in various countries or regions. However, globalization of research should be seen as having a much wider effect in the societies involved, in particular when we consider the public health, economic, social, and ethical implications.

The process of expanding the network of clinical research sites also fosters the integration and the development of

closer relationships among investigators at a global level. We consider this an essential element that should remain a prominent driver in this process.

In this article, we discuss recent trends in the globalization of clinical research in general and try to focus on some aspects particularly related to cancer research. As we address the underlying reasons for the phenomenon, we highlight some of the scientific and ethical concerns that have arisen as a consequence. Finally, some strategies to address and mitigate the challenges of conducting multinational clinical research are proposed.

GLOBALIZATION OF CANCER CLINICAL TRIALS

Cancer clinical research has historically been carried out in developed regions, particularly North America and Western Europe. Up to the 1980s, North American and European cooperative groups mostly sponsored by the National Cancer Institute (NCI) conducted most of the pivotal practice-changing trials. At that time, a progressive shift in the funding of research toward pharmaceutical companies was seen. In parallel, an increasing participation of research sites from countries outside North America and Western Europe was identified and has since transformed the development of new medications to what is now an increasingly globalized process.

Data from 15 global trial registries including more than 205,000 clinical trials conducted in 163 countries helps us to understand the dramatic changes in this area over the last few

KEY POINTS

- The nature of clinical research has changed substantially over the last 2 decades, evolving from being centered almost exclusively in developed countries to involve less developed regions of the world.
- Although early phase trials remain largely concentrated in the United States and Western Europe, confirmatory phase III studies have become increasingly global, sometimes with the largest proportion of patients being recruited in developing countries.
- Although the process of globalization should be considered largely unavoidable, we need to recognize both the advantages and the challenges associated with multiregional clinical trials.
- Both logistical and ethical implications of globalization of clinical research are important aspects to this discussion. In low- and middle-income countries, less people are dying from avoidable infectious diseases, and chronic noncommunicable illnesses are playing an increasing role in the mortality patterns justifying the inclusion of developing countries in global cancer studies.
- Although most of the discussion around globalization has been focused in pharmaceutical industry–sponsored research, efforts to integrate academic research at a global level are vital if we are going to succeed in advancing the science of medicine and improve health for all.

decades.[2] A 66% increase in the number of annually registered trials was identified comparing 2005 (introduction of International Committee of Medical Journal Editors registration requirements) and 2012. From 2005 through 2012, approximately 67% of the registered clinical trials were conducted in North America or Western Europe. The United States was the country with the single largest activity, conducting approximately 30% of the studies. However, the number of registered clinical trials has increased in all geographic regions during this time period, with the average annual growth greatest in the Asian (30%) and Latin American/Caribbean (12%) regions. During the same period, the average yearly increase was only 2% in North America.[2] These data indicate a large and unrealized potential for growth; the average clinical trial density (number of trials/population) of low-income countries averaged one clinical trial for every 3 million people, whereas Denmark demonstrated the highest density, with 107 trials for per 1 million individuals.[2]

Over the last decade, the number of U.S. Food and Drug Administration (FDA)–regulated clinical investigators has declined by 5.5% every year, whereas the percentage of investigators based outside the United States has grown yearly by an overall percentage of 15%. The annual growth has been 29% in Asia, 13% in Latin America, and 16% in Central and Eastern Europe.[3] A recent estimate indicates that one-third of all phase III trials sponsored by the 20 largest pharmaceutical companies are being conducted solely outside the United States.[4] Early trials seem to be conducted more frequently in North America (62%), whereas confirmatory trials are more frequent in Eastern Europe, Latin America, and Asia.[5] Data from ClinicalTrials.gov shows that over 70% of the registered cancer phase I trials are conducted in the United States, whereas less than 1% are conducted in Latin America. In larger registered phase III studies, 40% are conducted in the United States, 43% in Western Europe, and 17% in Latin America.[6]

Although pharmaceutical companies are sponsoring most of these multinational trials, we also have examples of increasing international cooperation in the academic research arena. The European Organization for Research and Treatment of Cancer (EORTC) has fostered clinical trials that bring together investigators and research groups from many different countries. The NCI and its cooperative groups have established guidelines for international collaboration.[7] The Breast International Group (BIG) has conducted large pivotal practice-changing studies that involved global participation and has recently launched an initiative addressing clinical research in Latin America organizing a retreat with the Latin American Cooperative Oncology Group (LACOG) and other research groups in the region (Argentine Group for Clinical Research in Oncology [GAICO], Uruguayan Oncology Cooperative Group [GOCUR], Peruvian Oncology Clinical Studies Group [GECOPERU], Brazilian Group of Breast Cancer Studies [GBECAM], Chilean Cooperative Group for Oncologic Research [GOCCHI]). The discussion identified major areas with need for improvement and gen-

erated a number of projects that will facilitate global integration and development of local expertise.[8] Although these are initiatives signaling a positive direction, they still fall short of what is really needed and a wider and more consistent international integration of academic research remains a challenge that should be addressed with much more emphasis in the future.

ASPECTS OF GLOBALIZATION OF CANCER CLINICAL TRIALS

Why Is Globalization Unavoidable?

In our opinion, a number of factors do contribute for this globalization trend to continue and increase in the foreseeable future. In Fig. 1, we attempt to didactically address the large number of issues that are part of this complex process. First, among many other factors, we need to consider the large number of patients required for confirmatory trials in the drug development process. Recruitment issues are undoubtedly one of the most important elements to take into consideration explaining the need for multinational trials. This has an important effect in shortening timelines in the drug development process. Recent statistics indicate that less than 5% of U.S patients actually participate in clinical trials.[9] In the United Kingdom, from 2001 through 2011 the National Cancer Research Network was able to boost recruitment in cancer trials with a substantial increase in participation from 3.7% to 17%.[10] Costly delays in recruitment are seen in 86% of trials, and in 94% of the studies the delay is more than 1 month.[11] Low accrual rates have a negative effect in the development of new therapies, as trials take

longer to achieve endpoints with consequent delays in the interpretation of the results and sometimes leading to early closure of studies with substantial waste of precious resources. Since accrual in developing countries can be 5 to 10 times faster than in the United States or Europe, globalization is no longer an option, but a dear necessity for sponsors.[12]

As an added and very important characteristic, patients enrolled in developing countries are more frequently treatment-naive and have less, or many times, no competing trials as alternatives.[13] Although this certainly represents a central and positive factor for certain studies, regional treatment availability has a number of other possible consequences that need particular attention and are discussed later in this article.

Another important driving aspect is the fact that the cost of running clinical trials in developing countries is lower than in developed countries. The cost of conducting clinical research in Brazil, Russia, India or China (BRIC countries) can be a fraction of what it would be in the United States or most Western European nations.[14] With the increased need for larger trials, lower operational costs are a crucial consideration. With the substantial savings obtained conducting trials in developing countries, increasingly, more phase II and phase III trials are being conducted in India and South America.[11]

Finally, in this era of personalized or precision medicine the need for small specific populations with a defined targetable marker will be a vital element to consider in the drug development process. The issue of variability in the frequency of a specific tumor subtypes in different populations or regions of the world is another important consideration.

FIGURE 1. Globalization of Cancer Clinical Trials
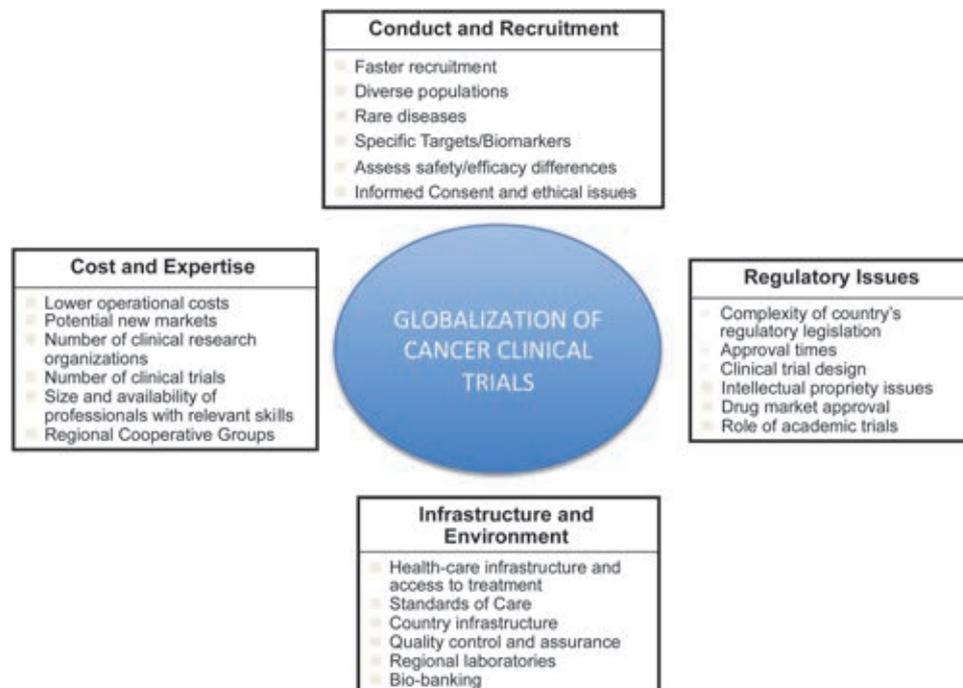
To appropriately address some tumor subtypes, we will need trials that will screen very large populations to identify specific patients. Globalization not only addresses this challenging point, but also allows for subgroup comparisons and other inferences.

What Are Some of the Advantages of Globalization of Clinical Trials?

Conducting clinical trials in developing countries may facilitate local product approval, thereby generating local drug prescription more quickly.[11] At the same time, it is very important to consider that globalization of clinical trials not only benefits the sponsor, but also global health. Expansion of clinical trials into developing countries brings new medical care options to subjects who may not even have the current standard of therapy available. In parallel, there are clear benefits to the local medical community that has earlier access and exposure to new drugs and therapeutic advances. Involvement of investigators from developing countries in the planning phases of the trial is essential as they may provide valuable contribution while being exposed to an experience that will have long lasting effects in the future development of regional studies. Other than addressing a question that interests a pharmaceutical company, developing a reliable research infrastructure and local expertise allows us to expect the development of locally coordinated research addressing pertinent regional health questions benefiting the local community.

What Are Some of the Challenges of Globalization of Clinical Trials?

The globalization of clinical trials raises logistical challenges that need particular attention. In Table 1, we present a few general suggestions to address some of the issues and help in the conduct of global trials; only some of them are addressed in the discussion. As a first consideration, we need to take into account the wide cultural differences among regions participating in international clinical trials. Although this can be seen as a positive consequence that will certainly enrich the process making results more widely applicable, cultural characteristics remain a very particular aspect that needs to be addressed from the inception of the trial. The perception of what clinical research is varies substantially across regions and populations, and may influence the willingness of subjects to participate in a study. Interpretation of placebo arms, local dietary habits, use of herbal medications or alternative treatment methods, adherence to treatment and other protocol procedures, and reporting of adverse events all can be perceived differently in different regions of the world. The patient-doctor relationship also varies across cultures and may have an effect in different aspects of care that can affect the results of a clinical trial.

One of the most central challenges of globalization relates to the regulatory aspect of running trials across borders with different legislations. Even though there are initiatives to harmonize regulatory legislation across regions and countries, it remains a very difficult objective to reach. Good clinical practice (GCP) harmonization has gone a long way and has been

TABLE 1. Addressing Some of the Challenges of Globalization of Clinical Trials

Problem	Solution
Regulatory Standards	Harmonize regulatory standards, processes, and procedures for the pharmaceutical industry (e.g., ICH, ICH Global Cooperation Group Members)
	Share science-based goals and standards for product safety, quality, and efficacy
Leveraging Knowledge and Resources	Use finite resources strategically and more efficiently, sharing knowledge and information, leveraging inspection resources (share inspection data, plan joint inspections, provide parallel advice to sponsors, organize regular discussions that increase communication)
Advancing Regulatory Science	Actively engage global partners to harness scientific development, resources, and brainpower to support science-based regulatory decision making and pursue the best possible public health solutions
Risk-Based Monitoring and Inspection	Use innovative strategies and tools to identify sites for clinical inspection (e.g., GCP risk-based site selection tool for clinical inspection)
Build Quality During the Planning Stages of Clinical Trials	Incorporate prevention strategies to avoid critical errors, and monitor for those errors
	In the planning stages of the protocol, consider potential regional variations in standards of care and the impact they may have in trial results
Central Laboratories and Bio-Banking	Decentralize laboratories developing regional expertise that will have significant "carry-over" benefits once the trial is completed
	Advance, harmonize, and simplify bio-bank regulatory issues
Invest in Research and Evidence-Based Cancer Care Relevant to Each Region	Characterize the epidemiology of disease in specific regions
	Create and strengthen national cancer registries
	Monitor local cancer outcomes and study the regional cost-effectiveness of specific interventions
	Build a clinical trials infrastructure that is sustainable and will support local/regional innovative research and educational opportunities
	Promote translational research initiatives

Abbreviations: ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; GCP, good clinical practices.

extremely successful in making possible the conduct of clinical research in different countries and health care scenarios. Although local regulatory standards may still vary, most respect the basic principles of GCP for clinical trials.

As quality is a fundamental principle in the conduct of clinical research, we need to address monitoring, auditing, and inspections as a basic element in the process of globalization. The mandatory requirement for GCP inspections in different parts of the world is costly, logistically challenging, and results in the need for qualified human resources. Barriers in communication (languages, dialects, and translation requirements), different qualification, interaction with national regulatory authorities, and confidentiality agreement issues are all very important considerations that can be difficult to address. As results are usually used to file for registration of new drugs, foreign data should be in accordance with FDA regulations.[15] Greater cooperation between national regulatory bodies and all involved in clinical research, including patient representatives, ethics committee, sponsors, and investigators needs to be stimulated to guarantee transparency in the whole process.

One other important aspect of globalization is the fact that the inclusion of geographically distinct populations with different lifestyles, ethnicities, and genetic profiles can influence the safety and efficacy of drugs. Global trials need to consider this genetic diversity, both when designing the study and at the time of interpreting or reporting the results. Safety concerns need to be taken into consideration, as several studies have shown that Asians metabolize drugs differently from other patients. As an example, for 31.2% of the new drugs approved in Japan between 2003 and 2005, the recommended standard doses were different from those in the Western population. In part as a result of this diversity, some countries like China and Japan require phase I trials to be performed in national subjects for all new drugs not already registered in another country.[16] As a consequence, early phase trials (usually performed in developed regions) are relatively more frequent there than in other countries. Another telling example comes from a study looking at the genetic makeup of the very heterogeneous Brazilian population, which demonstrated that well beyond self-characterization as white, brown or black, a large proportion of the population has substantial degrees of genetically defined African, Amerindian, and European ancestry with obviously important pharmacogenetic implications.[17] In our opinion, the explanation for this complex issue should widely link not only the genetic make-up of a population, but also take into account cultural and social differences in diet, way of life, education, physical activity, nutritional status, and religion, as they all could be contributing factors. Global studies should consider these important aspects that, in parallel, may represent a great opportunity to advance the investigation in this area.

Finally, a few words about the methodology and statistics of multiregional clinical studies. Global studies can answer global scientific questions and address global objectives, but at the same time they allow us to analyze regional aspects that could be extremely important. The ability of a study to reach a correct and robust conclusion depends heavily on a strong methodologic design and a careful sample size calculation, as well as planning a sampling strategy that could allow us to make inferences from specific populations.[18] The sample size calculation in a multiregional trial needs to take into account not only the overall sample size, but the influence that imbalances in regional recruitment may have in the interpretation of the results. In this sense, global trials, by expanding the population, can have both an extremely positive perspective of making inferences to a wider population, but at the same time, the danger of compromising the results because of problems with estimating the number of patients coming from a specific region.

A number of other issues should be considered when thinking about study design. The appropriateness of a global development strategy should be addressed or questioned if substantial regional variations in the results are to be expected. Different standards of treatment as well as differences in available supportive care could potentially have an effect in the results of a trial. Balancing enrollment or stratification according to region mitigates some of these potential imbalances; however, particular attention to these issues during trial design is mandatory. One issue that has been intensely discussed is the interpretation of the long-term survival results of some global trials. Regional variations in access to medications define different standards of care after progression in a study. This can and does have an important effect in survival estimations, as in many situations up to two-thirds or more of the survival of a certain population occurs after the patient has completed the trial and it can be expected that available treatments will be different depending on where the patient is from.[19]

Ethical Aspects of the Globalization of Clinical Trials

A number of ethical concerns have been appropriately raised in the process of globalization of clinical research. One of the main reasons to expand this debate is the fundamental need to protect subjects, regardless of where the clinical experiment is being conducted. Harmonization of ethical principles governing research, although different from the more standard and operational national regulatory legislation, still remains a challenge. Requirements for very specific, consistent, and clear documentation of the informed consent process are essential. Issues of language, cultural differences, illiteracy, and education should be constantly address.

The epidemiologic transition theory has focused in developing countries.[20] In low- and middle-income countries, less people are dying from avoidable infectious diseases as chronic noncommunicable illnesses are playing an increasing role in the mortality patterns. At the same time, we can identify changes in lifestyle behaviors and nutritional status with less nutrient deprivation and more obesity among the poorest populations. In addition, increases in life expectancy result in a higher proportion of older patients in these developing countries. All these epidemiologic conditions explain cancer as a global health care problem and justify the inclusion of patients from developing regions in global cancer studies.

One particular aspect that applies to most medium- and low-income developing countries is that participation in a clinical trial may represent the best therapeutic alternative for a specific patient, as the available standard of care or access to the health care system may be suboptimal. Although signing the informed consent can be interpreted as a reasonable attitude in this situation, the issue is the considerable difference this represents as we compare this situation with patients in other parts of the world where the standard of care is available outside a clinical trial. Recent research suggests that in a developing country like Brazil, financial gains and therapeutic alternative are the most frequent motivations explaining subject participation in clinical research.[21] The degree to which these elements represent nonperceived pressure that interferes with the consent process must be carefully considered while conducting research in less developed health care systems.

One particularly and very sensitive aspect of globalization of clinical research relates to what happens after the long and extremely expensive process of development, when a drug is proven as the better treatment alternative for a specific indication and is released into the market. Data presented by the European Federation of Pharmaceutical Industries and Associations breaking down sales of new medicines launched from 2009 through 2013 indicated that 55% were consumed exclusively in the United States, 23% in Western Europe, and 10% in Japan. This leaves 12% for the 6 billion people living in the rest of the world.[22] This fantastic heterogeneity in access has many implications and has not been appropriately addressed. Although the need to pay back the estimated more than 1 billion U.S. dollars it costs to develop a new medication is perfectly understandable, we should discuss how to make these pharmaceutical advances available to everybody who can benefit from it. Many of the institutions that participate in clinical research and generate data that helped with drug approval are not able to treat patients with the same medication after the trial is over and the drug is approved. These discrepancies in access are particularly striking when we look at a drug like imatinib that has changed the lives of patients with chronic myeloid leukemia and unquestionably can be characterized as the most successful targeted therapy to date. A recent publication suggests that less than 30% of the estimated 1.2 to 1.5 million patients with chronic myeloid leukemia had access to the drug 13 years after it was launched in 2001.[23] Whereas there are many other issues other than drug cost to explain this specific discrepancy, addressing the real value of a drug, much more than its price, is an urgent and inescapable debate.

The perception patients may have of what clinical research is also varies across different regions and is associated with educational and cultural characteristics that should be taken into account. Although the altruistic principles of participating in a phase I trial exist, data indicate that most patients do not have a clear understanding of the objective of the trial and accept entering the trial mainly expecting a therapeutic benefit. Analyses of predominantly early-stage cancer trials indicate that subjects are often motivated to participate in research by the expectation of a direct medical benefit, and when asked, blur the distinction between research and treatment. This therapeutic misconception has the clear potential of compromising the consent process. The subject knows it is research, but has an unrealistic expectation of being helped by the trial. For example, the investigator may think the chances of a subject benefiting from a phase I trial are remote (< 2%), but the patient thinks it may be as high as 50%. According to Kahneman, this may be an example where intuition (system 1) overwhelms logical thinking (system 2).[24] In one recently published report, 65 of 95 participants in phase I oncology trials did not know they were enrolled in a research study and 93% of them substantially underestimated their risk while overestimating their chances of benefit. Although the concerns of compromising consent have been heavily directed to developing countries where access to care, illiteracy, and language issues are substantial barriers, it is worth noting that these results refer to studies conducted in the United States.[25,26]

Looking from a wider perspective, the globalization of clinical research is an unavoidable process where the benefits do certainly exceed the potential challenges. Recent examples of trials with global participation have led to the development of fundamental advances in oncology. Among those, it is worth mentioning the development of anti-HER2 treatments that have improved the curability and survival of patients with the HER2-positive subgroup of breast cancer.[27-31] Another particular example is the fast development of crizotinib for the treatment of patients with ALK-positive non-small–cell lung cancer, in which global participation was instrumental to screen a large number of patients to identify the specific subgroup that benefits from crizotinib treatment.[32]

CONCLUSION

Globalization of clinical research is vital to speed up availability of life-saving medicines throughout the world. Challenges of conducting multiregional clinical trials can be successfully addressed through strategic and tactical planning as part of a global drug development program. Implementations of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines, particularly GCPs, do help standardize procedures and are instrumental to conduct trials at a global level.

Although some global initiatives have addressed biomedical education and suggested strategies to strengthen health care systems, we still need much more emphasis in the discussion of improving clinical research capacity with a worldwide perspective. Clinical trials are needed in low-income and middle-income countries to answer questions on prevalent conditions. At the same time, they improve local clinical research training and infrastructure, as well as facilitate early access to technology. The positive and lasting effects of global trials in less developed regions are certainly unquestionable but unfortunately yet to be realized. As more trials are conducted in resource-limited settings, good clinical practices

and ethical assurances must be secured. Human participation in clinical research is essential to advance medicine and public health, and expanding clinical trials mandates constant oversight to ensure research quality and protection of study subjects. Some decades ago, the development of global clinical research could have been considered a dream; it is now a pressing need that should be considered unavoidable in the future.

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DEVELOPMENTAL THERAPEUTICS AND TRANSLATIONAL RESEARCH

Improving Clinical Trial Efficiency: Thinking outside the Box

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Improving Clinical Trial Efficiency: Thinking outside the Box

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OVERVIEW

Clinical trial design strategies have evolved over the past few years as a means to accelerate the drug development process so that the right therapies can be delivered to the right patients. Basket, umbrella, and adaptive enrichment strategies represent a class of novel designs for testing targeted therapeutics in oncology. Umbrella trials include a central infrastructure for screening and identification of patients, and focus on a single tumor type or histology with multiple subtrials, each testing a targeted therapy within a molecularly defined subset. Basket trial designs offer the possibility to include multiple molecularly defined subpopulations, often across histology or tumor types, but included in one cohesive design to evaluate the targeted therapy in question. Adaptive enrichment designs offer the potential to enrich for patients with a particular molecular feature that is predictive of benefit for the test treatment based on accumulating evidence from the trial. This review will aim to discuss the fundamentals of these design strategies, the underlying statistical framework, the logistical barriers of implementation, and, ultimately, the interpretation of the trial results. New statistical approaches, extensive multidisciplinary collaboration, and state of the art data capture technologies are needed to implement these strategies in practice. Logistical challenges to implementation arising from centralized assay testing, requirement of multiple specimens, multidisciplinary collaboration, and infrastructure requirements will also be discussed. This review will present these concepts in the context of the National Cancer Institute's precision medicine initiative trials: MATCH, ALCHEMIST, Lung MAP, as well as other trials such as FOCUS4.

The traditional drug development paradigm of phase I for establishing the safety profile, followed by phase II for efficacy signal, followed by phase III for establishing definitive clinical benefit is challenged by the use of targeted therapeutics and incorporation of biomarker assessment for medical treatment.[1] Biomarkers are a critical component of targeted therapies as they can be used to identify patients who are more likely to benefit from a particular treatment. In this context of personalized medicine, a phase I study tests the methods of assessment of marker alteration in normal and tumor tissue samples and guides in the determination of cut points, and preliminary assessment of efficacy within molecularly defined subsets, a phase II study includes careful retrospective assessment of the marker to establish clinical value, and phase III trials are confirmatory in nature that validate the marker (and companion diagnostic) through large prospective, randomized, controlled trials (RCT) in a multicenter setting.[2] The fundamental challenge for development of new cancer therapeutics is therefore to be able to identify and assess activity in molecularly defined patient subsets starting from early phase trials to predict which patients will respond to a new agent/regimen.

Design strategies have evolved in the past few years as a means to accelerate this new drug development process so that the right therapies can be delivered to the right patients. Basket, umbrella, and adaptive enrichment strategies represent a class of novel designs for testing targeted therapeutics in oncology.[3] This review will aim to address the following, using examples of ongoing or completed trials to present the concepts: (1) when it is appropriate to use enrichment or targeted trial design strategies, (2) use of umbrella trials in improving clinical trial efficiency to assess the effect of different drugs on different mutations (molecular subtypes) within a single tumor type, and (3) the role of basket trials in screening agents efficiently to identify the "exceptional" responders, such as the effect of a single drug across multiple tumor types and/or histologic subtypes harboring the same mutation (molecular profile).

These design strategies challenge the historic paradigm of drug development. New statistical approaches, extensive multidisciplinary collaboration, and state of the art data capture technologies are needed to implement these strategies in practice. Logistical challenges to implementation arising from centralized assay testing, requirement of multiple specimens, multidisciplinary collaboration, and infrastructure requirements will also be discussed using illustrative examples where appropriate.

ENRICHMENT TRIAL DESIGNS

The enrichment design, also called targeted design, has become the most commonly used phase III design for codevel-

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FIGURE 1. Schematic Representation of the Enrichment Trial Design Strategy
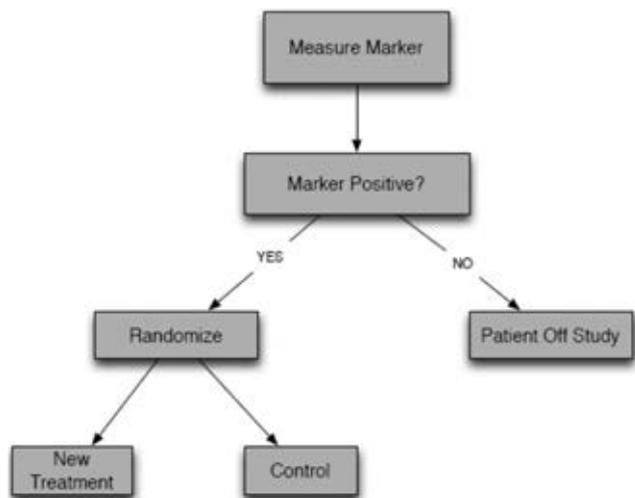
opment of a new cancer drug and a companion diagnostic. Patients are screened with the diagnostic test and those who are considered "test-positive" are eligible for the clinical trial. Eligible patients are randomized to receive either the test drug or an appropriate control regimen. In some cases, the randomization may be between the test drug and standard chemotherapy, or between standard chemotherapy alone versus standard chemotherapy plus the test drug. When there is no standard chemotherapy, the randomization may be

KEY POINTS

- Oncology is increasingly understood at the molecular level; therapeutic research has largely shifted from a focus of cytotoxic agents to newer targeted drugs that inhibit specific cancer cell growth and survival mechanisms.
- Novel clinical trial design strategies that challenge the historic paradigm of drug development are needed to accelerate the drug development process so that the right therapies can be delivered to the right patients.
- Patient selection and enrichment approaches are becoming increasingly relevant; however, sufficient biologic rationale, understanding of the mechanism of action of the drug, assay characteristics, and validated cut points are needed to support the enrichment strategy.
- Umbrella trials incorporate a central infrastructure for screening and identification of patients with a focus on a single tumor type or histology; multiple subtrials that test targeted therapeutics within molecularly defined subsets are embedded within the umbrella framework.
- Basket trial designs offer the possibility to include multiple molecularly defined subpopulations, across histologic subtypes or tumor types, in one cohesive design to evaluate the targeted therapy in question.

between the test drug and best supportive care. See Fig. 1 for a schematic of the enrichment trial design strategy.

Patients who are not marker-positive are not eligible for the study. Consequently, the design is best suited to settings where there is a strong biologic rationale or phase II data indicating that marker-negative patients are unlikely to benefit from the test drug. This was the case for the pivotal trials of vemurafenib for melanoma, in which the companion diagnostic was a sequencing test for a point mutation in the kinase domain of the *BRAF* gene.[4] It was also the case for crizotinib, in which the companion diagnostic was an assay for a translocation that activates the *ALK* gene.[5] One of the first uses of the enrichment design in oncology was for the pivotal trial of trastuzumab in women with metastatic breast cancer.[6] The companion diagnostic in that case was overexpression of the HER2 protein or amplification of the *HER2* gene. In these cases, there was a close linkage between the target of the test drug and the diagnostic test measuring a genomic alteration known to constitutively activate an oncogene target of the test drug. Kinase inhibitors generally have multiple targets; therefore, such drugs may be active for some patients who are test-negative. The proportion of patients who are test-negative who benefit from such a drug and the degree of benefit are generally much less than the treatment effect of the drug for test-positive patients. Hence, use of the enrichment design is appropriate. Test-negative patients can later be the focus of a separate clinical trial of the same drug after the drug is demonstrated to benefit those for whom it is designed to benefit. The test-negative patients can be spared the toxicity of a drug from whom few are expected to benefit.

One of the main benefits of the enrichment design is efficiency; that is, reduced sample size requirements.[7] The sample size of a clinical trial can generally be expressed in terms of the significance level, the statistical power, and the treatment effect to be detected with that power. For example, in comparing two treatments with regard to survival, the number of endpoint events, D, that must be observed can be written as:

$$D = 4\frac{(k_\alpha + k_\beta)^2}{(\log HR)^2}$$

where, for a two-tailed 5% significance level, $k_\alpha = 1.96$ and for power 90%, $k_\beta = 1.28$. The hazard ratio (HR) is a measure of the expected difference in the survival curve for the test treatment group and the control group. Broad eligibility clinical trials are frequently sized to detect 25% to 33% reductions in the hazard of death. Those reductions in hazard correspond to hazard ratios of 0.75 or 0.67, respectively. Using the natural logarithm in the above equation, the D value of 508 total events for HR equals 0.75. That is, 508 events must be observed in order to have 90% power for detecting a 25% reduction in hazard using a two-sided significance level of 5%. If, by the time of the final analysis only 25% of the patients are expected to fail, then to observe 508 events, one needs to accrue 2,032 patients. In contrast, we only need to have 90% power for detecting a 33% reduction in hazard, that is, a hazard ratio of 0.67, then expression[1] indicates that we only need

to observe 262 events instead of 508. Therefore, a slight change in the size of the treatment effect to be detected can lead to a large reduction in the sample size requirement.

If we preselect patients as in an enrichment design so that we expect an even larger reduction in hazard, such as 50%, then expression[1] indicates that we only need to observe 88 events. Targeting a larger treatment effect by enriching the population of the clinical trial to exclude patients unlikely to benefit from the test treatment can thus dramatically reduce the number of randomized patients required. However, the number of patients screened with the diagnostic test to obtain the required number of randomized patients may still be substantial.

To use the enrichment design, one should have strong biologic rationale or phase II data that test-negative patients are very unlikely to benefit from the treatment compared with the test-positive patients. One should also have an analytically validated test for use for selecting patients in the phase III clinical trial. Overexpression of the EGFR protein was thought to be a predictive biomarker for identifying patients who could benefit from erlotinib, but it was not used as an eligibility factor. It later turned out that mutation in the kinase domain of EGFR was the appropriate biomarker for erlotinib in NSCLC, not overexpression of the protein. Hence, it was useful that the initial phase III studies did not employ an enrichment design with EGFR overexpression as a selection factor. Another case in which the enrichment design was not used came in the development of the monoclonal antibodies panitumumab and cetuximab against EGFR in the treatment of advanced colorectal cancer.[8] Overexpression of EGFR was not used to restrict eligibility and it later turned out that the appropriate biomarker was KRAS mutation. Patients with mutated KRAS did not benefit from the antibodies because their tumors were not driven by EGFR activation, but patients with wild-type KRAS did benefit from the antibodies. Therefore, the enrichment design should be used primarily when the mechanism of the biomarker in the disease is well understood. It is also useful to have phase II data confirming that the understanding is correct.

EXTENSIONS OF ENRICHMENT DESIGNS
Run-in Designs
The enrichment design has been most effectively used with genomic alterations of the drug target as detected by the diagnostic test. Gene expression profiles have rarely been useful as predictive biomarkers for identifying which patients benefit from a specific drug therapy, although they sometimes have been useful prognostic indicators. For some drugs, such as antiangiogenic agents and immunologic agents, it has been difficult to identify pretreatment predictive biomarkers. Hong and Simon[9] showed how the enrichment design can sometimes be used after a short run-in phase on the test drug. During the run-in phase, a pharmacodynamic response, immunologic response, or early tumor response is measured. The patients are randomized after the run-in phase to either continuing the test drug or to switch-

ing to a control regimen. The biomarker measured during the run-in can be used to restrict eligibility to the randomization. A variation of this approach is to use the control regimen during the run-in phase and to only randomize patients who do not have a strong initial response to the control. This was used successfully in a clinical trial of dose-dense intensification of chemotherapy for patients with poor-prognosis germ cell tumors.[10]

Adaptive Enrichment Designs
A second extension of the enrichment design is the adaptive enrichment approach described by Simon and Simon.[11] For example, one may have a companion diagnostic test to use with the drug, but a cut-point for test positivity may not have been adequately determined based on phase II trials. With the adaptive enrichment design, one initiates the trial without using the test result to limit eligibility. Interim analyses adaptively restrict eligibility to increase the cut point of the test and exclude from eligibility the patients who do not appear to benefit from the test drug based on interim data for a short-term endpoint. The adaptive enrichment approach can also be used when there are multiple candidate biomarkers.

UMBRELLA TRIAL DESIGNS
Having a national network of clinical sites doing molecularly targeted clinical trials using a common genomic screening platform is an important defining characteristic of the umbrella design and is essential for effectively conducting targeted clinical trials in an increasingly stratified set of tumors. The umbrella infrastructure usually has the flexibility to add (or drop/modify) subtrials of molecularly targeted drugs and companion diagnostics based on accumulating evidence from the ongoing trial (and newly emerging data). The umbrella design is essentially two or more enrichment designs linked through a common patient screening infrastructure. Patients are screened for a specific set of biomarkers and assigned to a biomarker-driven substudy (targeted design) if it is determined that they have one of the target biomarkers. See Fig. 2 for a schematic representation of this design.

The Lung MAP (Master Protocol- phase II/III Biomarker-Driven Master Protocol for Second Line Therapy of Squamous Cell Lung Cancer; NCT02154490) study in squamous cell lung cancer is an example of an umbrella protocol that is currently open at hundreds of sites in the United States. The tumors of patients with advanced squamous cell lung cancer with one previous treatment are screened for genetic alterations in over 200 genes using a standardized sequencing platform. As a result of this tumor characterization, patients are recommended to one of five subtrials within the umbrella framework. Four of the five clinical trials are enrichment trials with eligibility limited to those patients whose tumor harbors a specified genomic alteration in a gene, which is a target of the test drug for that clinical trial. The fifth clinical trial is for patients whose tumor characterizations do not qualify them for one of the other four clinical trials. Each of the com-

FIGURE 2. Schematic Representation of the Umbrella Trial Design
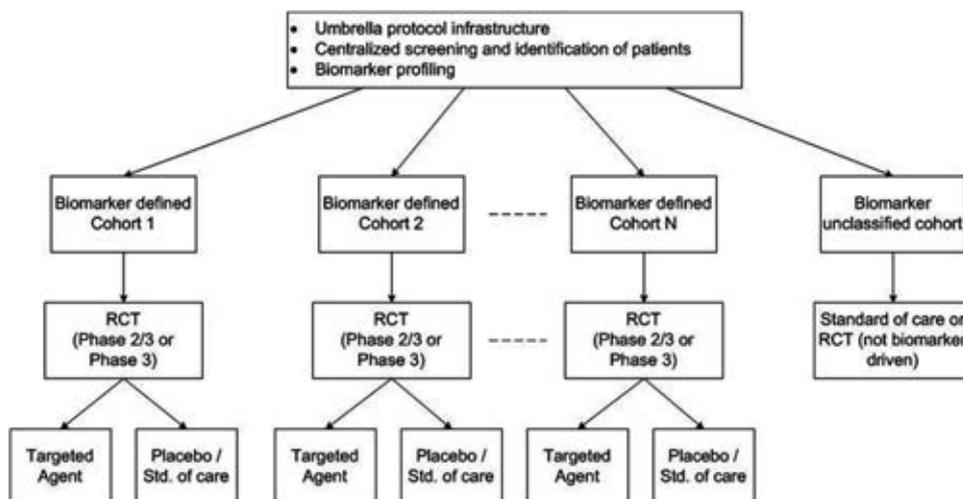
ponent clinical trials is a pivotal phase II/III clinical trial that can lead to the approval of a targeted drug with the genomic screening platform as companion diagnostic. Of note, a substantial amount of work is needed to analytically validate an assay to qualify it as a companion diagnostic. With the umbrella framework, this work qualifies the same platform for a large number of potential drugs.

The phase II/III design allows for early termination if the test treatment is not promising relative to the internal control based on progression-free survival (PFS) or may proceed to a phase III trial with PFS and overall survival (OS) as coprimary endpoints. The design within each substudy is standardized such that the phase II interim analysis is to occur on the observation of 55 progression events and the final phase III analysis is to occur on the observation of 256 deaths (provided the study proceeds to phase III). These are based on a phase II design with 90% power and 10% one-sided type I error to detect a two-fold increase in median PFS and a phase III design with 90% power and 1-sided 2.5% type I error to detect a 50% increase in median OS.

The ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial) clinical trial uses the umbrella design to identify and screen patients with the EGFR (approximately 15% prevalence) and ALK (approximately 5% prevalence) mutations in early-stage resected nonsquamous NSCLC. The surgical specimen will be tested centrally through a clinical laboratory improvement amendments (CLIA)–certified laboratory for specific genomic alterations in the *ALK* or *EGFR* genes. If an ALK-EML4 rearrangement is found, the patient will be referred to a double-blind, RCT comparing crizotinib with placebo adjuvant therapy. Patients with an activating mutation in EGFR will be referred to a double-blind RCT comparing erlotinib with placebo as adjuvant therapy. In the setting of these two parallel clinical trials studying resected NSCLC in a rare, molecularly-defined subsets of patients, a central protocol infrastructure for the identification of potentially eligible patients, and for central screening for appropriate geno-

types is valuable. Furthermore, ALCHEMIST includes a collection of tumor and blood specimens at baseline for genomic discovery efforts, and at the time of disease recurrence (optional tumor collection) to understand mechanisms of drug resistance and genomic evolution. Such advanced genomic analysis, performed on a clinically uniform and well-characterized NSCLC population, will allow for new insights into the relationship between tumor biology and clinical outcome. Thus, the ALCHEMIST screening platform consists of three integrated protocols: ALCHEMIST-Screening (A151216; NCT02194738), ALCHEMIST-EGFR (A081105; NCT02193282), and ALCHEMIST-ALK (E4512; NCT02201992).

An estimated 8,000 patients will be screened through A151216 to facilitate accrual to the two substudies: ALCHEMIST-EGFR and ALCHEMIST-ALK. Both subtrials are harmonized in terms of primary endpoint (OS), as well as with regard to many of the trial logistics (eligibility criteria, follow-up schedule during treatment, and long-term follow-up, etc.). The ALCHEMIST-EGFR trial has a target accrual of 410 patients, with centrally-confirmed EGFR mutation status, to have at least 85% power to detect an HR of 0.67 in favor of the erlotinib arm, using a one-sided type I error rate of 5%. The ALCHEMIST-ALK trial has a target accrual of 378 patients, with centrally-confirmed ALK status, to have at least 80% power to detect a 33% reduction in the OS HR of 0.0105 to 0.0070 in favor of the crizotinib arm, using a one-sided type I error rate of 5%. As with the Lung MAP protocol, ALCHEMIST is set up to accommodate the addition of subtrials of targeted therapeutics in this setting if and when they are ready to be tested in a phase III setting.

Another example of the umbrella trial design is the FOCUS4 Master Protocol (molecular selection of therapy in colorectal cancer: a molecularly stratified RCT program).[12] It is an integrated protocol with parallel, molecularly stratified, randomized comparisons of maintenance therapies for patients with advanced or metastatic colorectal cancer after receiving first-line chemotherapy. It includes randomized phase II/III trials following the principles of the multi-arm

multi-stage[13,14] (MAMS) design for predefined molecular cohorts. Similar to Lung MAP, for patients whose biomarker panel results are unclassifiable or for those whose molecular cohort is temporarily not open for recruitment, and for any patients unable or unwilling to travel, a concurrent nonbiomarker-driven trial comparing capecitabine against no treatment is available. Four prespecified interim analyses are planned for each trial: stage I (assess safety), stage II (assess lack of benefit), stage III (assess efficacy for PFS), and stage IV (assess efficacy for OS). Stages I and II mirror a conventional phase II trial design, and stages III and IV are similar to a phase III trial design paradigm.

BASKET TRIAL DESIGNS

The discovery of driver oncogenes and the corresponding successful development of therapies targeting those genetic abnormalities have dramatically impacted clinical research, placing great focus on the biologic causes of dramatic responses to therapy among populations that do not derive treatment benefit overall. The first observation of this phenomenon was the discovery that imatinib effectively targets the BCR-ABL tyrosine kinase in chronic myeloid leukemia; this was subsequently followed by the discovery that EGFR mutations in NSCLC confer dramatic responses to treatment with gefitinib.[15-18] When an exceptional responder is observed, often referred to as the n-of-one phenomenon, further investigation of the tumor biology and the therapeutic mechanism of action may lead to formally testing a predefined hypothesis, which is that patients whose tumor harbor a particular genetic aberration respond to a specified targeted agent in the context of a prospective clinical study. Basket trials have come to be known as an efficient way of screening experimental therapeutics across multiple patient populations in early-phase drug development. Basket trials generally assign treatments to patients based on the molecular alterations that their tumors contain, regardless of the histologic type of the tumor. Like umbrella trials, there may be a common genetic screening platform, especially if the cohorts defined by the study are histology-independent and defined

only by the presence of a single molecular aberration; however the term basket trial has also been used to describe studies in which patients are assigned to cohorts by their cancer type. Whether cohort eligibility criteria are histology- or mutation-specific, these trials are generally conducted within the context of a single protocol. Figure 3 provides a generic representation of a basket trial design schema. There is perceived efficiency in running multiple cohorts in this way, since conducting a stand-alone study within each cohort separately would be exponentially more resource-intensive.

However, basket trials are not without their limitations. Paramount to their conduct is a strong scientific rationale for the molecular marker-drug pairing, as well as reliable assay development for the marker of interest. Genomic variants have unknown or differential variability across tumor types,[19] and there is often uncertainty about whether a particular mutation in a tumor of a particular histologic type should be considered actionable for treatment with a given drug. Resolving these uncertainties, however, is the reason for doing the study. These trials often study cancers so rare that it may be impossible to study them in a randomized setting, and usually require coordination and participation from multiple institutions to meet accrual objectives.[20] They can depend heavily on tumor availability for genetic screening, which can be difficult to obtain or to ethically justify in certain types of cancer. This design also depends on the availability of a sufficient number of drugs targeting diverse deregulated pathways.

Basket trials are discovery trials and there has been uncertainty about how to design such trials statistically. Consequently, in some basket trials, justification of sample sizes has been absent despite increased interest in efficacy endpoints, such as response, and the amendment process is frequently used to expand cohorts to sample sizes that would otherwise be sufficient for the proper conduct of a randomized phase II or III study.[21,22] The practice of not justifying sample size is particularly worrisome since it counters the intent of minimizing the number of patients exposed to toxic or ineffective drugs, and in light of this, investigators should consider early stopping rules and provide clearly defined criteria for study completion.[21] Additional steps should also be taken to ac-

FIGURE 3. Schematic Representation of the Basket Trial Design

- Single protocol infrastructure
- Enroll to multiple cohorts defined by genetic mutation and/or cancer type
- Centralized screening and patient identification according to cohort eligibility criteria
- Single-arm statistical designs to support relatively exploratory or early drug development hypotheses

Cohort 1 patients matched to Drug 1

Cohort 2 patients matched to Drug 2

Cohort 3 patients matched to Drug 3

Cohort X patients matched to Drug X

knowledge the effect of patient and tumor heterogeneity on the numerical variability of results and the multiple comparisons issues that arise as a result of excessive testing of subgroups during the conduct of these trials.

The Molecular Analysis for Therapy Choice (MATCH) study is an example of a basket trial being led by the ECOG-ACRIN Cancer Research Group, along with the National Cancer Institute, and is slated to activate within the National Clinical Trials Network this year.[23] As many as 3,000 patients with refractory solid tumors or lymphoma and for whom no standard treatment prolonging survival exists will be screened with the goal of accruing approximately 35 patients (31 eligible) in as many as 20 to 25 biomarker-defined subgroups. Targeted agents for this trial were selected if: (1) a drug is U.S. Food and Drug Administration (FDA)–approved for a malignant indication and there is a molecular abnormality that can serve as a valid predictive marker, (2) the drug is investigational, but met a clinical endpoint (such as PFS or tumor response) in any malignancy, has evidence of target inhibition, and has evidence of a predictive molecular marker, and (3) the drug is investigational, but has demonstrated clinical activity in any malignancy and evidence of target inhibition, and has evidence of a predictive molecular marker.

Patients who are enrolled into the MATCH trial are assigned to histology-independent subgroups and treated with the agents matched to their tumor's identified molecular abnormality. If a patient's tumor harbors more than one molecular abnormality identified as actionable for treatment in MATCH, then treatment will be assigned based on the mutation detected in a higher percent of tumor cells; if this percentage is within 15% for two or more aberrations in more than one pathway, then the patient will be assigned to the treatment with fewer patients enrolled, or if equally enrolled, the patient will be randomized between the treatments under consideration.

The primary endpoint of each cohort is objective response (OR) rate and 6-month PFS. OR will be compared to a historic control of 5%, whereas 6-month PFS will be compared to a historic control of 15%. This design provides 92% power to test the alternative hypothesis that a drug confers an OR rate of 25% and 89% power that a drug provides a 6-month PFS rate of 38% while controlling the type I error rate at the one-sided 0.05 level. If the OR rate is greater than or equal to five out of 31 patients (16%) or PFS at 6 months is greater than or equal to nine out of 31 patients (29%), then an agent will be considered promising and worthy of further testing. For each arm, there is a futility rule provided as a guideline; an interim analysis will be performed after 15 eligible patients have been enrolled. If no response is observed among these patients and the 6-month PFS is two out of 15 patients or less (13%), the analysis result will be presented to the steering committee for further guidance on whether the arm should be stopped early.

CONCLUSION

The fundamental assumption of precision medicine is that using the genetic makeup of the tumor and the genotype of the patient will enable targeted therapeutics to improve clinical outcomes.[3] Although there have been notable successes with this approach, the methods for matching drugs to tumors is still rudimentary and numerous challenges remain to be addressed adequately. These include an understanding of the interaction of signaling pathways, the clonal evolution and heterogeneity of tumors, ability to obtain tumor biopsies (often multiple and over time), technical limitations with assays, centralized molecular testing, adequate resources and infrastructure for a quick turnaround of biomarker results to make these designs feasible, and effective multidisciplinary collaborations. Nevertheless, genomic technology has already become a part of routine clinical practice. Enrichment, umbrella, and basket trial designs are gaining popularity as they present novel strategies to accelerate the drug development process so that the right therapies can be delivered to the right patients quickly.

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DEVELOPMENTAL THERAPEUTICS
AND TRANSLATIONAL RESEARCH

Overcoming Drug Resistance in Targeted Therapy of Cancer

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Overcoming Resistance to Anti-EGFR Therapy in Colorectal Cancer

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OVERVIEW

Our understanding of the genetic and nongenetic molecular alterations associated with anti–epidermal growth factor receptor (EGFR) therapy resistance in colorectal cancer (CRC) has markedly expanded in recent years. Mutations in *RAS* genes (*KRAS/NRAS* exons 2, 3, or 4) predict a lack of clinical benefit when anti-EGFR monoclonal antibodies (mAbs) are added to chemotherapy. Genetic events in additional nodes of the mitogen-activated protein kinase (MAPK)–phosphoinositide 3-kinase (PI3K) pathways that bypass EGFR signaling, such as *BRAF* or *PIK3CA* mutations or *KRAS*, *ERBB2*, or *MET* amplifications, also may confer resistance to cetuximab or panitumumab. Polymorphisms that block antibody binding as a result of EGFR extracellular domain mutations have been reported. Nongenetic mechanisms, including compensatory activation of receptor tyrosine kinases HER3 and MET, together with high expression of the ligands amphiregulin, transforming growth factor alpha heregulin, and hepatocyte growth factor in the tumor microenvironment also are thought to be involved in resistance. In one-third of the samples, more than one genetic event can be found, and nongenetic events most likely coexist with gene alterations. Furthermore, activation of a gene expression signature of epithelial-mesenchymal transition has been associated with reduced cellular dependence on EGFR signaling. Collectively, this body of work provides convincing evidence that the molecular heterogeneity of CRC plays an important role in the context of resistance to anti-EGFR therapy. Herein, we discuss how this knowledge has been translated into drug development strategies to overcome primary and acquired anti-EGFR resistance, with rational combinations of targeted agents in genomically selected populations, second-generation EGFR inhibitors, and other agents expected to boost the immune response at the tumor site.

Colorectal cancer is the third most common cancer type in Western countries, and mortality as a result of CRC has declined progressively in recent decades.[1] This can be attributed not only to cancer screening programs but also to the availability of more effective therapies, both for early-stage and advanced disease. Extensive investigations have uncovered several critical genes and pathways relevant to CRC initiation and progression. The knowledge about these driver molecular alterations has already translated into drug development and biomarker discovery, with EGFR being the most noticeable example. The specific genetic background of the tumor largely influences the efficacy of anti-EGFR therapies. Nearly 70% of CRC samples have heterogeneous genetic alterations in genes involved in EGFR signaling, which negatively affect response to the mAbs cetuximab and panitumumab. Furthermore, molecular heterogeneity of CRC has been recognized as pivotal in the evolution of clonal populations during anti-EGFR therapies.[2] In this manuscript, we summarize the current understanding about primary (de novo) and secondary (acquired) resistance to anti-EGFR thera-

pies in metastatic CRC (mCRC) and about emerging predictive biomarkers that could ultimately help define the optimal combination therapy for patients in routine clinical practice.

PRIMARY RESISTANCE TO ANTI-EGFR THERAPY IN ADVANCED CRC

Only 10% of patients with chemotherapy-refractory mCRC achieve objective responses to cetuximab or panitumumab as single agents.[3,4] In this setting, *KRAS* mutations in codons 12 and 13 (exon 2) were the first to be causally implicated in primary resistance to anti-EGFR mAbs.[5,6] Cetuximab and panitumumab provide similar overall survival benefit in *KRAS* exon 2 wild-type, chemotherapy-refractory mCRC.[7] Furthermore, in the first- or second-line settings, patients whose tumors harbor *KRAS* exon 2 mutations do not benefit from the addition of anti-EGFR mAbs to chemotherapy, providing compelling evidence of primary resistance.[8-11]

Because not all patients with *KRAS* wild-type disease benefit from targeted agents, many groups investigated addi-

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tional biomarkers of resistance that could explain the heterogeneity in clinical response. The next step was to evaluate additional oncogenic events in the MAPK pathway. Approximately 20% of CRC samples harbor activating mutations in *BRAF* (V600E), *NRAS* (codons 12, 13, 59, 61, 117, and 146 in exons 2, 3, and 4), or rare variants in *KRAS* (codons 59, 61, 117, and 146 in exons 3 and 4). Retrospective studies indicate that these events could also underlie resistance to single-agent cetuximab or panitumumab in patients with chemotherapy-refractory mCRC.[12,13] More recently, randomized studies have shown that mutations in *KRAS* exons 3 and 4 or *NRAS* exons 2, 3, and 4 can also predict a lack of clinical benefit of anti-EGFR mAbs when given in combination with chemotherapy in the first-line setting.[14-16] Patients with CRC that is wild type for all *RAS* mutations (*KRAS* and *NRAS* exons 2, 3, and 4) showed higher response rates and overall survival when cetuximab or panitumumab, versus bevacizumab, was combined with standard chemotherapy. The *BRAF* V600E mutation, conversely, did not predict resistance to first-line anti-EGFR mAbs plus chemotherapy.[8,14] However, *BRAF* mutation is a strong marker of poor prognosis in mCRC. Interestingly, in the second-line setting, the addition of panitumumab to irinotecan had a detrimental effect on survival of a *BRAF* mutant population.[17] It is expected that combinations of anti-EGFR mAbs and selective *BRAF* inhibitors, which have had unprecedented response rates in early clinical trials,[18,19] may overcome this negative effect.

KEY POINTS

- EGFR is a validated target for cancer therapeutics, with cetuximab and panitumumab leading to significant overall survival benefits when added to first-line chemotherapy in patients with genomically selected (all *RAS* wild type) metastatic colorectal cancer.
- Multiple genetic alterations driving resistance to anti-EGFR monoclonal antibodies have been described, with significant overlap in primary and secondary resistance mechanisms, supporting clonal selection as a major determinant of the final outcome.
- Resistance to anti-EGFR therapy in colorectal cancer is also related to nongenetic mechanisms, such as compensatory activation of parallel receptor tyrosine kinases and overexpression of ligands involved in paracrine signaling networks in the tumor microenvironment.
- Increased knowledge of anti-EGFR resistance mechanisms has guided the development of effective therapies, with promising second-generation antibodies and combinations with pan-ERBB, the MET signaling pathway, or MEK inhibitors.
- The immune system has a crucial role in modulating response to monoclonal antibody therapy in cancer, with novel agents inducing potent cytotoxicity and combinations with immune checkpoint inhibitors worth exploring in the anti-EGFR resistance setting.

Molecular alterations in additional nodes of the EGFR pathway also seem to confer primary resistance to targeted therapies. Among them, *PIK3CA* exon 20 mutations and *PTEN* alterations, which frequently coexist with *RAS* mutations, have been associated with unresponsiveness to anti-EGFR mAbs.[12,20,21] Gene expression signatures that correspond to *KRAS*-, *BRAF*-, and *PIK3CA*-activating mutations predict efficacy of anti-EGFR therapy, suggesting that a shared downstream component of these pathways mediates resistance.[22] Moreover, *KRAS, ERBB2*, and *MET* amplifications have been shown to bypass EGFR signaling and activate the pathway.[23-26] The rarity of these gene amplifications and the relatively small sample size of each study preclude assessment of their clinical value as negative predictive biomarkers of response to anti-EGFR mAbs.

Additionally, the extensive crosstalk among the ERBB family of receptors leads to upregulation of parallel pathways after blockade of a particular receptor as a compensatory adaptive mechanism. One potential mechanism of resistance to anti-EGFR therapy in mCRC is related to the ability of EGFR to form heterodimers with HER3, which results in downstream PI3K and MAPK activation.[27-29] MET signaling also appears to cooperate with the EGFR pathway to promote the growth of CRC cells.[30,31] Signals produced by either the cancer cells themselves or by stromal fibroblasts, such as hepatocyte growth factor (HGF), activate parallel receptor tyrosine kinase (RTK) pathways that render CRC cells insensitive to anti-EGFR therapy.[31] These pathways may offer primary escape mechanisms, allowing tumors to circumvent one pathway that has been pharmacologically blocked.

Temporal heterogeneity has also been assessed as a potential mechanism of primary resistance to anti-EGFR therapy. However, when considering matched primary and metastatic samples not previously exposed to targeted agents, the mutational statuses of *KRAS, NRAS, BRAF*, and *PIK3CA* are highly concordant, exceeding 90%.[32] In fact, the effectiveness of the anti-EGFR mAbs in *RAS* wild-type CRC has largely been documented in trials that identified genetic mutations in archived diagnostic samples rather than in new biopsies from metastatic lesions. Importantly, mutations in *KRAS, NRAS*, and *BRAF* tend to be mutually exclusive at baseline samples.

Drug Development to Overcome Primary Resistance to Anti-EGFR Therapy

The first approach to increase the efficacy of anti-EGFR mAbs tested in the clinic was the combination with vascular endothelial growth factor receptor (VEGFR) pathway inhibitors. Despite positive effects on progression-free survival and objective response, cetuximab plus brivanib (a VEGFR multikinase inhibitor) increased toxicity and did not improve overall survival in patients with chemotherapy-refractory, *KRAS* wild-type mCRC.[33] Similarly, the addition of panitumumab or cetuximab to bevacizumab and oxaliplatin-based chemotherapy in the first-line setting did not improve outcomes in patients with *KRAS* wild-type disease.[34,35] These results raise the possibility of a negative interaction (pharma-

cokinetic and/or pharmacodynamic) between the targeted agents as well as an increased risk of toxicity, leading to frequent treatment delays and reduced dose intensity.

Our current knowledge about primary resistance to cetuximab and panitumumab in mCRC, summarized in Fig. 1A, has led to more promising drug development strategies. Quadruple-negative (*KRAS/NRAS/BRAF/PIK3CA* wild-type) tumors, which represent up to 30% of cases, are more likely to respond.[12] On the basis of preclinical data and early clinical trials, this type of tumor is particularly sensitive to dual-EGFR targeting (ERBB tyrosine kinase inhibitors [TKIs] added to anti-EGFR mAbs),[36] and this strategy is undergoing clinical validation, as shown in Table 1. The important role of compensatory HER3 signaling and PI3K pathway activation in the development of resistance to anti-EGFR mAbs also has been translated into clinical trials. Results of a randomized, phase II trial in chemotherapy-refractory, *KRAS* wild-type, anti-EGFR–naive mCRC also suggest a role for MET pathway targeting; the combination of an anti-HGF mAb and panitumumab led to higher response rates and a trend for a better outcome in the population with MET-overexpressing tumors.[37] Another strategy to overcome resistance in this setting is to boost the immune response by increasing the numbers of immune cells engaging in antitumor activity.[38] A growing body of preclinical and clinical evidence shows that the immune system contributes substantially to the thera-

peutic effects of mAbs in vivo.[39] The combination of immune modulators or checkpoint inhibitors with cetuximab is under evaluation as a first-line therapy of *KRAS* wild-type mCRC.

SECONDARY RESISTANCE TO ANTI-EGFR THERAPY IN ADVANCED CRC

The most common molecular mechanisms that drive secondary resistance to anti-EGFR mAbs in mCRC comprise genetic alterations known to confer primary resistance to cetuximab or panitumumab, as illustrated in Fig. 1B. *KRAS* and *NRAS* mutations, mostly affecting exons 3 and 4, were found to emerge in a significant proportion of tumor biopsies and circulating tumor DNA (ctDNA) from patients who had acquired resistance to anti-EGFR mAbs.[40-43] In one-third of patients, multiple genetic events coexisted in the same sample.[41,42] *BRAF* and *PIK3CA* mutations also were found in biopsies of patients who experienced relapse, although all of these mutations were absent in samples from the same patients at the beginning of the treatment.[42] Multiple repeated biopsies revealed that the percentage of mutant alleles increased under drug exposure and became undetectable after drug withdrawal.[44] These findings suggest that a clonal selection process achieved under treatment pressure plays a major role in determining the final clinical outcome. In addition to acquired PI3K and MAPK downstream mutations, *ERBB2* or *MET* gene amplifications also were described as drivers of acquired resistance to anti-EGFR therapy in cell models and patient samples.[24-26,45] Likewise, these events in RTKs leading to parallel signaling activation are enriched in post-treatment biopsies compared with primary tissues. Moreover, acquired *EGFR* extracellular domain mutations (exon 12) that disrupt cetuximab binding but may be permissive for interaction with panitumumab have been identified recurrently in cetuximab-treated mCRC samples with secondary resistance.[44,46,47] Of note, by using a highly sensitive sequencing technology, *EGFR* S492R was found in 16% of patients after cetuximab exposure and in only 1% after treatment with panitumumab.[47] This mechanism is analogous to other secondary genetic alterations in the target oncoprotein that perturb the conformational state of the kinase drug-binding sites and render the receptor insensitive to the drug (e.g., erlotinib/gefitinib and *EGFR* T790M).

Nongenetic mechanisms also have been linked to anti-EGFR resistance in mCRC. In biopsies from patients who experience disease progression while receiving cetuximab or panitumumab therapy, only a fraction of cells carry activating MAPK mutations, which suggests that wild-type cells also can survive the treatment. Preclinical findings point to the conservation of EGFR dependency in tumors that progressed during anti-EGFR therapy, most likely related to adaptive ligand overexpression.[48] Increased secretion of EGFR ligands amphiregulin and transforming growth factor alpha (TGF alpha) by limited *KRAS* mutant clones has been proposed as a paracrine resistance mechanism to anti-EGFR mAbs in CRC models.[49] In addition, ectopic production of HGF by stromal cells renders CRC cell lines insensitive to

FIGURE 1. Resistance to Anti-EGFR Therapies in Advanced CRC
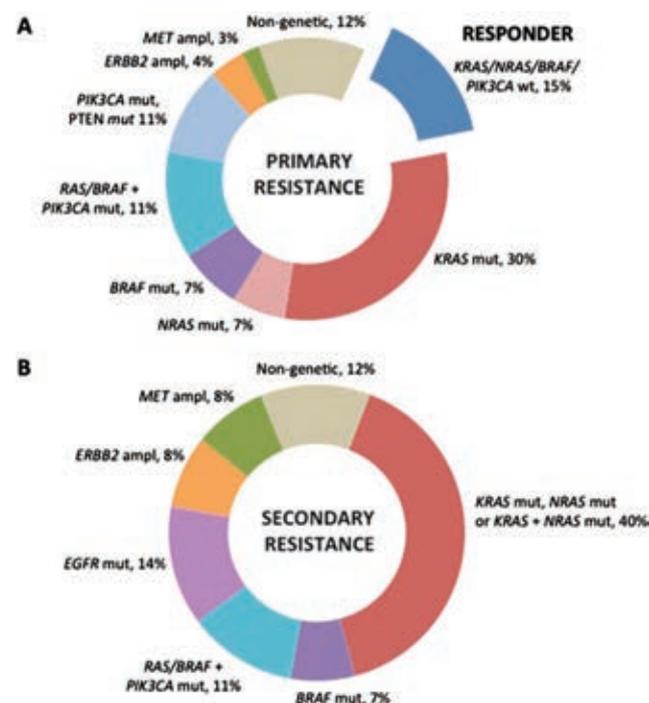
(A) Genomic alterations linked to primary (de novo) resistance. Separated from the chart are quadruple-negative tumors, which have higher chances of response. (B) Secondary (acquired) resistance mechanisms, suggesting clonal selection as the major determinant of the final outcome.

Abbreviations: EGFR, epidermal growth factor receptor; CRC, colorectal cancer; ampl, amplified; mut, mutated; wt, wild type.

TABLE 1. Resistance Mechanisms to Anti-EGFR Therapies and Drug Development Strategies in Advanced CRC

Setting	Mechanism of Resistance	Strategy	Example	Trial
First-Line Anti-EGFR Therapy	**Nongenetic**			
	KRAS/NRAS/BRAF/PIK3CA wt	Anti-EGFR mAb + chemotherapy	Panitumumab + FOLFIRI	NCT01704703 (phase II)
	Immune evasion	Anti-EGFR mAb + immune checkpoint inhibitor	Cetuximab + pembrolizumab	NCT02318901 (phase I/II)
		Anti-EGFR mAb + immune modulator	Cetuximab ± complement receptor 3 modulator	NCT01309126 (phase III)
	Compensatory pathway activation			
	ERBB family receptors	Anti-EGFR/HER3 mAbs	MEHD7945A + FOLFIRI versus cetuximab + FOLFIRI	NCT01652482 (phase II)
		Anti-EGFR mAbs + irreversible ERBB TKIs	Cetuximab ± afatinib	NCT01919879 (phase II)
	PI3K-mTOR	Anti-EGFR mAbs + mTOR inhibitors	Panitumumab + everolimus + irinotecan	NCT01139138 (phase I/II)
Progressing in Third-Line Setting After Response to Anti-EGFR Therapy in First-Line Setting	**Nongenetic**			
	KRAS/NRAS/BRAF wt	Anti-EGFR mAb + chemotherapy (rechallenge)	Cetuximab + irinotecan-based therapy	NCT02296203 and NCT02316496 (phase II)
Acquired Resistance to Anti-EGFR Therapy	**Nongenetic**			
	KRAS/NRAS/BRAF/PIK3CA wt	Anti-EGFR mAbs + irreversible ERBB TKIs	Cetuximab + neratinib	NCT01960023 (phase II)
	Sustained EGFR addiction			
		Novel anti-EGFR mAbs	Sym004 versus investigator's choice	NCT02083653 (phase II)
	Genetic			
	ERBB2 amplification	Dual anti-EGFR/HER2 therapy	Trastuzumab + pertuzumab or lapatinib	Heracles trial (phase II)
	MET amplification	Anti-EGFR mAbs + MET inhibitors	Cetuximab + INC280	NCT02205398 (phase II)
	RAS mutations	Anti-EGFR mAbs + MEK inhibitors	Panitumumab + MEK162	NCT01927341 (phase II)
	EGFR mutations (S492R, K467T)	Panitumumab (if resistance to cetuximab), Sym004	Not available	Not available

Abbreviations: EGFR, epidermal growth factor receptor; CRC, colorectal cancer; wt, wild type; mAb, monoclonal antibody; FOLFIRI, fluorouracil, leucovorin, and irinotecan; TKIs, tyrosine kinase inhibitors; PI3K, phosphoinositide kinase-3; mTOR, mammalian target of rapamycin.

EGFR blockade.[31] An autocrine loop with the HER3 ligand hereglulin also has been associated with acquired resistance to cetuximab.[28] These experiments suggest that the relative expression of growth factor ligands in the tumor microenvironment and that a cross-talk driven by resistant subpopulations can relay redundant survival pathways and impair responsiveness to kinase inhibitors.

Drug Development to Overcome Secondary Resistance to Anti-EGFR Therapy

The first strategy to overcome acquired resistance to anti-EGFR mAbs in mCRC tested in the clinic was treatment with an alternative antibody. Panitumumab has minimal benefit in patients with KRAS wild-type mCRC who have experienced progression while receiving cetuximab as prior therapy.[50,51] Differences in response rates reported in small cohorts may be related to the inclusion of patients without objective disease progression while receiving cetuximab or for whom cetuximab-containing regimens may have been ceased as a result of toxicity in the absence of disease progression. In both circumstances, re-treatment with panitumumab is expected to demonstrate some degree of clinical

activity. Recently, with the hypotheses that the effect of pharmacologic treatment represents a selective pressure and that (preexisting) sensitive subclones may emerge after treatment breaks, the idea of re-exposure to anti-EGFR therapies has been revisited. As shown in Table 1, clinical trials are prospectively evaluating rechallenge with anti-EGFR mAbs in the third-line setting after a response to targeted therapies in the first-line setting. To increase the chances of treatment benefit, only patients with KRAS/NRAS/BRAF wild-type disease are being enrolled.

Second-generation anti-EGFR mAbs engineered to induce enhanced antibody dependent cell-mediated cytotoxicity (ADCC) or increased receptor internalization/downregulation also have been tested in the context of acquired resistance to cetuximab or panitumumab.[48,52-54] Imgatuzumab (GA201) is a dual-acting mAb glycoengineered for enhanced ADCC in addition to EGFR signaling inhibition, which has demonstrated superior preclinical in vivo efficacy to cetuximab in both KRAS wild-type and KRAS mutant xenograft models.[52] Although promising clinical efficacy was seen in a phase I trial of patients with mCRC,[52] a recently presented, randomized, phase II study comparing imgatuzumab with

cetuximab in *KRAS* exon 2 wild-type or with irinotecan-based chemotherapy alone in patients with *KRAS* exon 2 mutant disease has not shown any improvement in survival outcomes.[53] Another example is Sym004, a combination of two chimeric mAbs targeting nonoverlapping epitopes of the EGFR extracellular domain III designed to induce a much higher degree of receptor degradation. Encouraging results have been observed in the expansion of the phase I trial, with one-third of patients with anti-EGFR–refractory mCRC experiencing significant tumor shrinkage and prolonged disease stabilization.[54] This suggests that the dependency on EGFR ligands remains an oncogenic driver in this setting. Sym004 is under clinical evaluation in a randomized, proof-of-concept, phase II study in patients with *RAS* wild-type mCRC that is refractory to anti-EGFR mAbs.

Because acquired anti-EGFR resistance may result from compensatory signaling through ERBB receptors, cetuximab was investigated in combination with pertuzumab (an HER2 heterodimerization inhibitor) in patients with cetuximab-resistant *KRAS* wild-type mCRC (irrespective of *ERBB2* amplification). In a phase I trial, this regimen was not tolerated because of overlapping toxicities, but partial responses and disease stabilization were reported in some patients.[55] The results of clinical trials evaluating alternative combinations in genomically selected populations are highly anticipated.

When a genetic mechanism for secondary resistance is identified, promising strategies under investigation include the combination of anti-EGFR mAbs with MEK inhibitors (when *RAS* mutant clones emerge) or with HER2- or MET-targeted therapy (in the context of acquired receptor amplification). In principle, a parallel RTK pathway may be activated by compensatory ligand overexpression (nongenetic mechanisms), and the efficacy of these combinations may not be restricted to tumors with gene amplifications. Patients who have tumors that show the *EGFR* S492R mutation at relapse could be offered panitumumab-based therapy (in the setting of resistance to cetuximab), because panitumumab binds to a distinct epitope of the molecule. Indeed, investigators published a case report of a 5-month clinically beneficial response.[46] The novel anti-EGFR mAb Sym004 is active in preclinical models of acquired *EGFR* extracellular domain mutations.[44]

RESISTANCE TO ANTI-EGFR THERAPY IN EARLY-STAGE CRC

The improved survival with anti-EGFR mAbs added to chemotherapy in patients with *RAS* wild-type mCRC was the basis for exploring the role of targeted therapies in the adjuvant setting. However, two studies with cetuximab added to standard chemotherapy in stage III colon cancer did not show improved survival outcomes.[56,57] Although the reasons for these negative findings are not known, divergent effects of anti-EGFR therapy in early-stage versus advanced-stage CRC reinforce the theory that micrometastases behave differently than clinically apparent foci of metastatic disease. In one trial

(PETACC-8), a subgroup analysis showed that chemotherapy plus cetuximab was only advantageous for high-risk patients who had pT4pN2, which suggests that they resembled patients who have advanced disease.[56] Investigators also have raised the possibility of a negative interaction between the antibody and oxaliplatin. There is limited clinical evidence from a subgroup analysis (study N0147) suggesting that irinotecan could have been a better choice for combination with cetuximab.[58] Another interesting explanation comes from preclinical experiments that show reduced cellular dependence on EGFR signaling when a tumor cell has transitioned to a mesenchymal phenotype, which is known to support invasion and metastatic seeding of carcinomas.[59] In line with this hypothesis is the finding that early-stage CRC tumors with intrinsic mesenchymal signatures have reduced benefits from treatment with anti-EGFR mAbs given at the time of relapse.[60,61] In preclinical models, mesenchymal CRC cell lines were particularly sensitive to MET inhibitors.[60]

CONCLUSION

The elucidation of de novo and acquired resistance mechanisms arising in the setting of targetable tumor dependencies is guiding the development of rational therapeutic strategies. It is likely that a combination of targeted therapies will be necessary to effectively prevent and/or treat drug-resistant cancers. Colorectal tumors that initially respond to and then relapse after anti-EGFR targeted therapy eventually become highly molecularly heterogeneous. The significant overlap of genetic events associated with primary and secondary resistance supports clonal selection linked to tumor heterogeneity as a major determinant of treatment outcome. It also indicates that the same therapies used for acquired resistance— that is, salvage regimens— could be potentially useful in upfront therapy. The ultimate goals are to increase the magnitude and/or duration of clinical response and to delay the emergence of resistance when such combinations are administered as initial therapy. As recently highlighted by Misale et al,[2] the plethora of alterations that emerge at relapse biochemically converge to activate the EGFR/*RAS*/MAPK pathway (i.e., convergent evolution), which may facilitate drug development strategies in this setting.

Knowledge of the specific genetic mechanisms of drug resistance and the compensatory parallel signaling activation that occurs during anti-EGFR exposure have been fundamental for the study of alternative kinase inhibitors. Examples include combinations of pan-ERBB, MET, or MEK inhibitors with anti-EGFR mAbs, both in first-line and refractory settings, with promising results in early clinical trials. An alternative approach is to develop second-generation inhibitors of the oncoprotein. For a subset of mCRC tumors, this strategy also has been proven efficacious clinically, but the mechanisms underlying the sensitivity, such as sustained EGFR addiction as a result of ligand overexpression or increased ADCC at the tumor site, are still unknown.

Furthermore, because targeted gene analysis does not always explain the mechanism by which CRC becomes resis-

tant to anti-EGFR therapy, we believe that additional research should be directed toward understanding and controlling the evolutionary process in tumors, paying particular attention to gene expression profiling and interactions with the immune system and microenvironment. Incredible technological developments (e.g., ctDNA targeted sequencing) and advances in drug design will enable treatments that are precisely targeted to the unique molecular characteristics of an individual's cancer. However, until comprehensive mo-lecular profiles of individual tumors becomes feasible, it will be challenging to determine the presence of all of these modifiers of therapy efficacy in clinical practice. Finally, for successful drug translation to the adjuvant setting and increase curability of early-stage CRC, it is imperative to understand the micro- and macroenvironments in which targeted agents exert their effects and also to assess the activities of targeted agents with different chemotherapy backbones in preclinical models of early versus late-stage disease.

Disclosures of Potential Conflicts of Interest

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Resistance to Anti-HER2 Therapies in Breast Cancer

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OVERVIEW

HER2 is amplified or overexpressed in 20% to 25% of breast cancers. HER2 is a redundant, robust, and powerful signaling pathway that represents an attractive therapeutic target. Anti-HER2 therapy in the clinic has resulted in significant improvements in patient outcomes and, in recent years, combinations of anti-HER2 therapies have been explored and carry great promise. However, treatment resistance remains a problem. Resistance can be mediated, among others, by pathway redundancy, reactivation, or the utilization of escape pathways. Understanding mechanisms of resistance can lead to better therapeutic strategies to overcome resistance and optimize outcomes.

HER2 is a member of a membrane tyrosine kinase receptor family (HER1–4). Although HER2 does not have any known ligands, there are more than 10 different ligands that activate other family receptors (Fig. 1).[1-7] On binding, ligands induce receptor homo- and heterodimerization activating a phosphorylation-signaling cascade. HER2 in cancer cells can be activated by either heterodimerization with other ligand-bound HER family members or, when overexpressed, by homodimerization.[8] The resulting downstream signaling regulates transcription of genes responsible for cell proliferation, survival, angiogenesis, invasion, and metastasis.[1-4,6,9,10]

HER2 is amplified or overexpressed in 20% to 25% of breast cancers and results in aggressive behavior with rapid growth and frequent metastasis. Therefore, targeting HER2 represents an attractive treatment option, and that approach has been successful in the clinic.

The first targeted therapy against HER2 was the humanized monoclonal antibody trastuzumab. The mechanism of action of trastuzumab is not completely understood but it interacts with the extracellular domain of HER2 to inhibit its function. Trastuzumab has been suggested to inhibit signaling from HER2 homodimers better than heterodimers with HER1 (epidermal growth factor receptor [EGFR]) or HER3.[11-13] The resulting downregulation of the PI3K/AKT pathway signaling leads to induction of apoptosis in human tumors.[6,9,14] Trastuzumab has also been shown to work in part by inducing antibody-dependent cellular cytotoxicity. Although trastuzumab combined with chemotherapy reduces the risk for recurrence of HER2-positive tumors, many patients have tumors that exhibit de novo or acquired resistance.[15-18]

Many mechanisms for resistance to anti-HER2 therapy with trastuzumab have been suggested.[18,19] Those broadly fall under three major categories. The first category is redundancy within the HER receptor layer: the ability of the pathway to continue to signal despite being partially inhibited because of redundant ligands and receptors that enable alternative dimerization patterns. The second category is reactivation: the ability to reactivate pathway signaling at or downstream of the receptor layer such as with activating HER or downstream mutations, or loss of downstream pathway negative-regulating mechanisms. The third category is escape: the use of other pathways, which may pre-exist or be acquired at the time of resistance, but are not usually driving the cancer cell when HER2 is uninhibited. For purposes of this review, we will give an example from each of those resistance categories, focusing on mechanisms of resistance that have been best explored preclinically and in clinical trials: incomplete receptor family inhibition as an example of redundancy, deregulation of the PI3K pathway as an example of reactivation, and the role of the estrogen receptor (ER) in resistance as an example of escape. Additional roles for multiple other pathways and mechanisms involved in intrinsic and acquired resistance to HER-targeted therapy, including various receptor and cellular tyrosine kinases (e.g., MET, IGFR-1, c-SRC, and EphA2),[19-23] mucins,[24] regulators of cell cycle and apoptosis[19,25-27] and various elements of the tumor microenvironment and the host immune system,[28-31] have been recently thoroughly reviewed,[18] and are beyond the focus of the current paper.

INCOMPLETE RECEPTOR FAMILY INHIBITION

One mechanism for resistance to anti-HER2 therapy is incomplete blockade of the HER receptors. This occurs when the drug or drugs used do not effectively block signaling from

FIGURE 1. HER Pathway Signaling Network
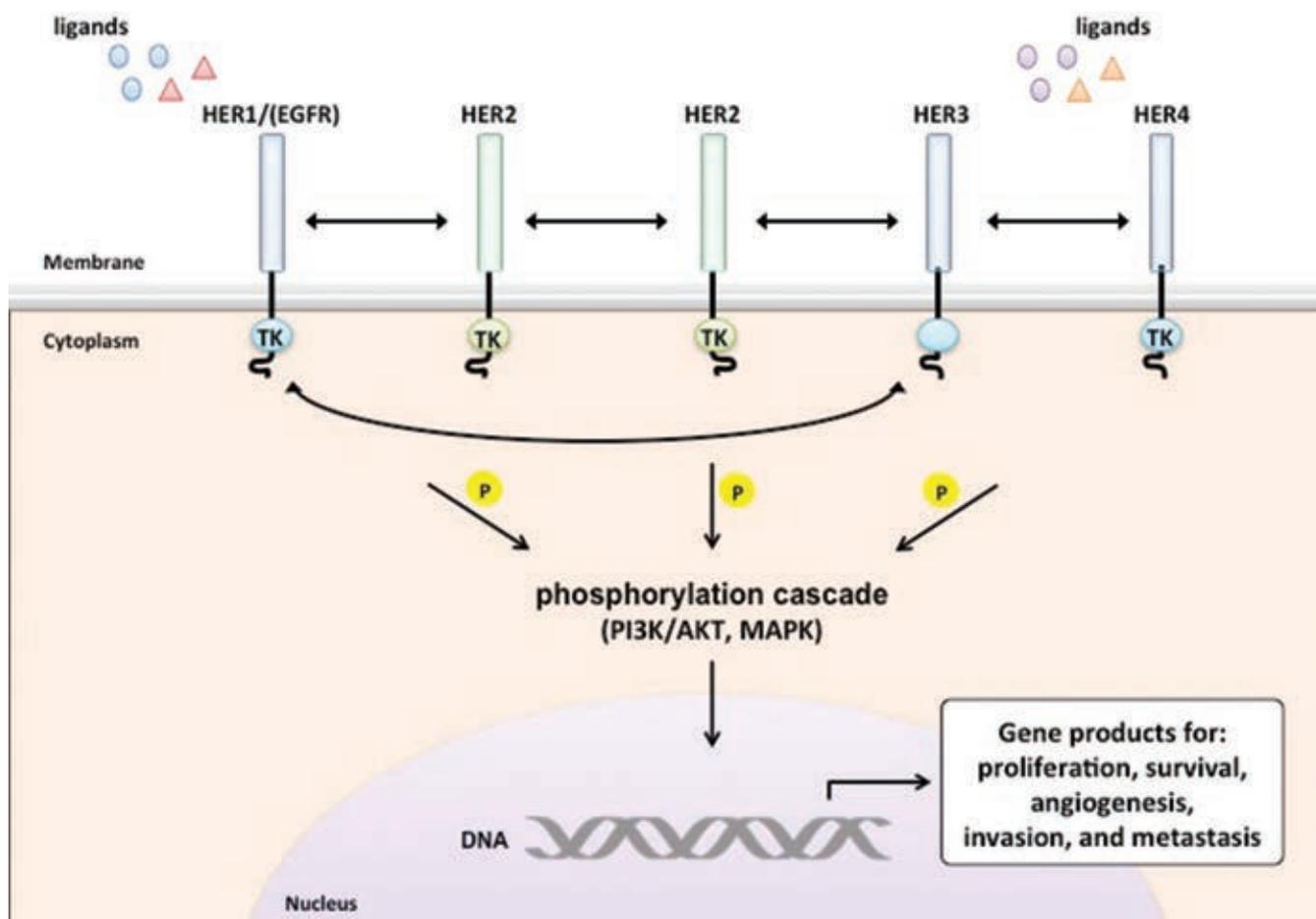
HER2 is a member of the HER network consisting of three additional transmembrane receptor tyrosine kinases, HER1 (epidermal growth factor receptor [EGFR]), HER3, and HER4 plus more than 10 ligands. HER2 is the only receptor member for which a specific ligand has not been identified; whereas, HER3 lacks intrinsic kinase activity. On ligand binding, HER receptors form homodimers or heterodimers that, after transphosphorylation of their kinase domains, trigger downstream signaling cascades via key intermediates such as the phosphatidylinositol-3 kinase (PI3K)/AKT and the RAS/mitogen-activated protein kinase (MAPK) pathways. Activation of these downstream signaling intermediates promotes the expression of genes involved in tumor cell proliferation, survival, angiogenesis, invasion, and metastasis. HER2 is the preferred heterodimerization partner for other HER proteins and HER2/HER3 is considered the most oncogenic heterodimer. When HER2 is gene-amplified and/or overexpressed (20% of breast cancers), it can also be activated by homodimerization.

all HER family dimer pairs and, thus, do not fully inhibit downstream signaling. Several preclinical studies have explored regimens that more completely block HER2 as the major driver pathway and increase efficacy of anti-HER2 therapy by using combinations of targeted agents.

In addition to trastuzumab, several other drugs are available to inhibit the HER receptor layer more completely. Table 1 lists these inhibitors, with a focus on key agents that are already in clinical use or that have been rigorously investigated alone or in combination in preclinical and clinical studies of HER2-positive breast cancer. Pertuzumab binds to the heterodimerization domain of HER2 and blocks its interaction with HER1 and HER3.[32] Lapatinib, afatinib, and neratinib are dual kinase inhibitors (HER1, HER2).[33] T-DM1 (ado-trastuzumab emtansine) is an antibody-drug conjugate.[34] Gefitinib and erlotinib are potent kinase inhibitors of HER1.[35]

In animal models, various doublet and triplet combinations for HER2-positive tumor xenografts were studied. One

KEY POINTS

- Successful targeting of HER2 has improved outcomes in HER2-positive breast cancer, but treatment resistance remains a problem.
- Treatment resistance can be caused by pathway redundancy, pathway reactivation, or escape pathways.
- Use of combination anti-HER2 treatments for potent inhibition of the HER family signaling is biologically sound and offers great clinical promise.
- Estrogen receptor (ER) is a potential resistance pathway to anti-HER2 treatments. Concomitant inhibition of ER with potent HER2 inhibition is being investigated in clinical trials.
- PI3K pathway activation is also a potential mechanism of resistance and represents another attractive therapeutic target to overcome or prevent anti-HER2 treatment resistance.

TABLE 1. Key Monoclonal Antibodies and Small Molecules Targeting HER Family Receptors

Drug	Category	Mechanism	Phase of Development
Pertuzumab	Monoclonal antibody	HER2 dimerization inhibitor	Clinically available
T-DM1	Antibody-drug conjugate	Microtubule polymerization inhibitor; ADCC	Clinically available
MM-121	Monoclonal antibody	HER3-targeted antibody	II
MM-111	Monoclonal antibody	Bispecific antibody targeting HER2/HER3	I
Afatinib	Small molecule	Irreversible pan-HER tyrosine kinase inhibitor	III, available for lung cancer
Neratinib	Small molecule	Irreversible pan-HER tyrosine kinase inhibitor	III
Gefitinib	Small molecule	EGFR tyrosine kinase inhibitor	Development stopped
Erlotinib	Small molecule	EGFR tyrosine kinase inhibitor	Available for lung cancer

Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; EGFR, epidermal growth factor receptor; T-DM1, trastuzumab-derivative of maytansine.

study showed that the three-drug combination of gefitinib, pertuzumab, and trastuzumab, which blocks signaling from all HER1, HER2, and HER3 receptor homo- and heterodimer pairs, is much more effective than any of the single agents or two-drug combinations like trastuzumab and pertuzumab. The combination was capable of eradicating HER2 overexpressing xenografts in mice.[36] Two other studies showed that the two-drug combination of lapatinib and trastuzumab was also effective in eradicating HER2 over-expressing xenografts.[37,38] Interestingly, inhibition of HER1 (EGFR) activity increased efficacy even though this receptor is expressed at very low levels in some of these models. In ER-positive tu-

mors, endocrine therapy was also required for optimal antitumor effects.[36,37] Moreover, these studies showed that even lower drug doses and intermittent therapy with this lapatinib/trastuzumab regimen was effective in eradicating most tumors.[37]

These and other studies provided a strong biologic rationale for clinical trials that combined two anti-HER2 agents (dual inhibition). These trials showed increased efficacy when combined with chemotherapy in the metastatic setting,[39,40] and improved outcomes for patients. This approach was also extensively studied in the neoadjuvant and adjuvant setting, with some trials still ongoing.

TABLE 2. Randomized Neoadjuvant Trials Testing Dual HER2-Targeted Therapy in Combination with Chemotherapy[42-47]

Study	Phase	Patient Population	No. of Patients	Regimen Chemotherapy	Anti-HER2 Therapy	Duration (Weeks)	pCR (%)
NeoALTTO	III	Operable BC, T2-4*	455	Paclitaxel	Trastuzumab	18	29.5
					Lapatinib		24.7
					Trastuzumab + lapatinib		51.3
NSABP B-41	III	Operable BC	519	AC → paclitaxel	Trastuzumab	28	53.5
					Lapatinib		52.5
					Trastuzumab + lapatinib		62.0
CALGB 40,601	III	Operable BC, stage II-III	305	Paclitaxel	Trastuzumab	16	46
					Lapatinib		-
					Trastuzumab + lapatinib		56
TRYPHAENA	II	Operable BC, stage II-III**	225	FEC → docetaxel	Trastuzumab + pertuzumab	18	61.6
					Trastuzumab + pertuzumab		57.3
				Carboplatin + docetaxel	Trastuzumab + pertuzumab		66.2
CHER-LOB	II	Operable BC, stage II-IIIA	121	Paclitaxel → FEC	Trastuzumab	26	25.0
					Lapatinib		26.3
					Trastuzumab + lapatinib		46.7
NeoSphere	II	Operable BC, T2-4	417	Docetaxel	Trastuzumab	12	29.0
					Pertuzumab		24.0
					Trastuzumab + pertuzumab		45.8

Abbreviations: BC, breast cancer; AC, doxorubicin and cyclophosphamide; CALGB, Cancer and Leukemia Group B; CHER-LOB, Chemotherapy Herceptin and Lapatinib in Operable Breast Cancer; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; NeoALTTO, Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimization; NeoSphere, Neoadjuvant Study of Pertuzumab and Herceptin in Early Regimen Evaluation; NSABP, National Surgical Adjuvant Breast and Bowel Project; pCR, pathologic complete response; Pts, Patients.
*Excluding inflammatory breast cancer.
**Including inflammatory and locally advanced (no prior chemotherapy).

TABLE 3. Completed and Ongoing Neoadjuvant Trials Testing Dual HER2-Targeted Therapy without Chemotherapy[43,49,66]

Study	Phase	No. of Patients	Regimen		pCR
			Hormonal Therapy	HER2-Targeted Therapy	
NeoSphere	II	107	None	Trastuzumab + pertuzumab	17%
TBCRC 006	II	64	Estrogen deprivation for ER-positive tumors*	Trastuzumab + lapatinib	27%
TBCRC 023	II	33	Estrogen deprivation for ER-positive tumors*	Trastuzumab + lapatinib 12 weeks	12%
		61		Trastuzumab + lapatinib 24 weeks	28%
PAMELA	II	150	Estrogen deprivation for ER-positive tumors**	Trastuzumab + lapatinib 18 weeks†	Not available

Abbreviations: ER, estrogen receptor; NeoSphere, Neoadjuvant Study of Pertuzumab and Herceptin in Early Regimen Evaluation; TBCRC, Translational Breast Cancer Research Consortium; pCR, pathologic complete response; Pts, patients.
*In combination with ovarian suppression in premenopausal women.
**Letrozole or tamoxifen according to patient's menopausal status.
†Paclitaxel will be added to dual HER2 blockade if tumor progression is observed by ultrasound at week 6.

In the neoadjuvant (or preoperative) setting, combination anti-HER2 therapies have been investigated to directly test the hypothesis that more potent inhibition of the HER2 pathway would increase treatment efficacy, as suggested by the preclinical evidence discussed above.[36,37,41] Serial tumor biopsies obtained from patients on these trials also provide an invaluable resource to explore mechanisms of resistance and biomarkers of response. Some of the important clinical trials that tested this concept are summarized in Table 2.[42-47] These trials investigated the addition of a second anti-HER2 agent, namely lapatinib or pertuzumab, to trastuzumab plus chemotherapy. All of these trials used pathologic complete response (pCR), an endpoint that has variable definition and some limitations in correlation to outcomes. However, it is an endpoint that the U.S. Food and Drug Administration (FDA) has sanctioned as grounds for drug approval.

These neoadjuvant dual inhibition trials generally showed similar results: that combining dual inhibitors of HER2 with chemotherapy is a more effective strategy than trastuzumab plus chemotherapy as measured by pathologic complete response. The trials that utilized pertuzumab plus trastuzumab as their anti-HER2 therapy led to FDA approval of pertuzumab in the neoadjuvant setting in combination with trastuzumab and chemotherapy.

However, first results from the ALTTO trial[48] did not confirm results reported in the neoadjuvant trials (Neo-ALTTO and NSABP B-41).[42,44] The ALTTO trial is a study of more than 8,000 women randomly assigned to receive adjuvant trastuzumab, lapatinib, their sequence, or their combination. The study showed no significant difference in disease-free survival between patients who received trastuzumab only or those who received trastuzumab plus lapatinib at median follow-up of 4.5 years.[48] There are many possible factors that may have contributed to these results, including the high percentage of patients with small and node-negative tumors (40% each), and the use of aggressive chemotherapy (anthracyclines and taxanes), which might abrogate or mask benefit from dual inhibition. The results of the APHINITY trial, a randomized trial of adjuvant trastuzumab compared with trastuzumab plus pertuzumab plus chemotherapy, are eagerly awaited. So far, results from ALTTO[48] argue that dual

inhibition combined with chemotherapy is not for everyone and proper patient selection based on clinical and biologic characteristics is important. It also argues for a de-escalation strategy that carefully selects appropriate therapy for patients, and for switching more toxic treatment like chemotherapy (at least in part, and in some patients) with less toxic treatment, like targeted therapy.

As part of that de-escalation strategy, another approach that is biologically sound and clinically less toxic is to target HER2-positive tumors with potent anti-HER2 targeted agents without chemotherapy. Table 3 summarizes results from the trials that explored this concept, most notably, NeoSphere (targeted therapy alone arm: pertuzumab plus trastuzumab) and TBCRC 006 (lapatinib plus trastuzumab, with endocrine therapy if ER-positive).[43,49] Both of these trials showed that, in a subgroup of patients, pCR can be achieved in a proportion of patients without chemotherapy. It is important to use tissue acquired through serial tumor biopsies in these trials to identify molecular markers that can help determine which patients may benefit from a targeted therapy alone approach. It is clear that chemotherapy plays an important role in improving outcomes for many patients. The challenge remains to identify which group is which.

The drug trastuzumab emtansine (T-DM1), an antibody-drug conjugate is a first-in-class agent where molecules are attached to the antibody trastuzumab by a linker. On binding, the compound is internalized. This way, the drug would achieve the goal of inhibiting HER2, while delivering a cytotoxic agent to the cancer cell, theoretically enhancing efficacy and decreasing toxicity.[34] T-DM1 performed well in clinical trials in the second-and third-line treatment of HER2-positive metastatic breast cancer,[50,51] and as a result was approved for that indication by the FDA. This drug is currently being studied in the first-line setting in metastatic disease and in early-stage curable HER2-positive breast cancer. The MARIANNE trial randomized 1,095 patients to one of three arms: a taxane plus trastuzumab (the standard of care at the time the study was designed), T-DM1, and T-DM1 plus pertuzumab. A recent press release from the manufacturer stated that neither of the T-DM1-containing arms achieved

FIGURE 2. Reported *PIK3CA* Mutation Analyses in Neoadjuvant Trials of HER2-Targeted Therapy[56-58]
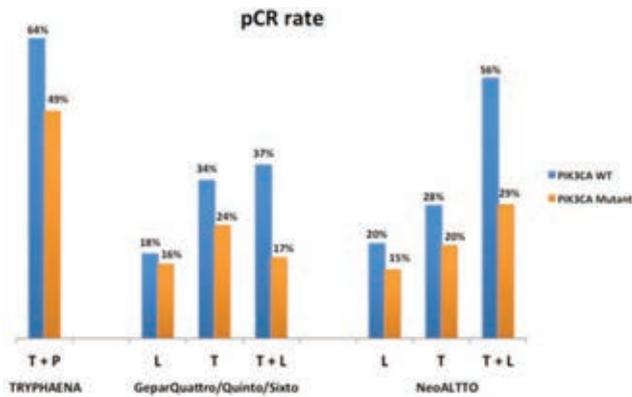
The percentage of patients who obtained a pathologic complete response (pCR) are reported for each treatment arm (L, lapatinib; P, pertuzumab; T, trastuzumab). Orange bars represent patients harboring *phosphatidylinositol-3 kinase* (*PIK3CA*) mutations; blue bars represent patients with *PIK3CA* wild type (WT).

superiority compared with trastuzumab plus a taxane. Results are expected to be presented at the 2015 ASCO Annual Meeting. Close examination of these results is important but, so far, it appears that T-DM1 will remain as a therapeutic option for HER2-positive metastatic breast cancer that is resistant to first-line chemotherapy plus trastuzumab and pertuzumab. Further investigation into the mechanism of action of T-DM1 and how best to combine it with other agents is warranted.

ACTIVATION OF THE PI3K PATHWAY

The phosphoinositide 3-kinase (PI3K)/AKT pathway is a powerful downstream signaling pathway activated by HER2

signaling. Constitutive activation of the PI3K/AKT pathway by reduced levels of its tumor suppressor PTEN or by activating mutations in PIK3CA results in resistance to trastuzumab and other anti-HER2, according compelling preclinical evidence.[52,53] Activation of PI3K signaling by enrichment or emergence of *PIK3CA* mutations may also contribute to acquired resistance to lapatinib in experimental models.[54] Other studies, however, suggest that PTEN status may not affect sensitivity of HER2-positive breast cancer cells to lapatinib.[55]

This mechanism of resistance has been explored in clinical samples. Tumor tissue samples acquired at baseline from patients who participated in neoadjuvant clinical trials with anti-HER2 agents were studied for *PIK3CA* mutations, and some trials also examined expression of PTEN.[56-58] As shown in Fig. 2, these trials consistently showed that patients with tumors that harbor an activating *PIK3CA* mutation have a lower chance of achieving pCR after neoadjuvant therapy with anti-HER2 agents. This difference seems to be more notable in the group of patients who received dual anti-HER2 inhibitors compared with those who received a single anti-HER2 agent. Although the majority of these studies co-administered chemotherapy, which may confound their results, there are concordant results from TBCRC006,[58] a neoadjuvant clinical trial in which patients with HER2-positive breast cancer received dual anti-HER2 therapy alone, allowing for a purer biologic signal. This trial also demonstrated that *PIK3CA* mutations or low PTEN levels are associated with treatment resistance.

Conflicting results were reported, however, about the role of PTEN in resistance to HER2-targeted therapies in other clinical trials. Reasons for these conflicting results may po-

TABLE 4. Impact of Hormone Receptor Status on Pathological Complete Response Rate in Neoadjuvant Studies with HER2-Targeted Therapies[42,43,45,49,67]

Study	No. of Patients	Regimen		Overall pCR Rate (%)	pCR rate According to HR (%)	
		Concurrent Therapy	Anti-HER2 Therapy		HR+	HR−
NeoALTTO	455	Paclitaxel	Trastuzumab	29.5	22.7	37.5
			Lapatinib	24.7	16.1	33.7
			Trastuzumab + lapatinib	51.3	41.6	61.3
GEPARQUINTO	620	EC → docetaxel	Trastuzumab	30.3	25.8	38.7
			Lapatinib	22.7	16.2	28.3
NeoSphere	417	Docetaxel	Trastuzumab	29.0	20	36.8
			Pertuzumab	24	17.4	30
			Trastuzumab + pertuzumab	45.8	26	63.2
		None	Trastuzumab + pertuzumab	16.8	5.9	29.1
TRYPHAENA	225	FEC → docetaxel	Trastuzumab + pertuzumab	61.6	49	65
			Trastuzumab + pertuzumab	57.3	46	79
		Carboplatin + docetaxel	Trastuzumab + pertuzumab	66.2	50	84
TBCRC 006	64	Letrozole* for ER-positive pts	Trastuzumab + lapatinib	27	21	36

Abbreviations: ER, estrogen receptor; HR, hormone receptor; NeoALTTO, Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimization; EC, epirubicin/cyclophosphamide; NeoSphere, Neoadjuvant Study of Pertuzumab and Herceptin in Early Regimen Evaluation; pCR, pathological complete response; TBCRC, Translational Breast Cancer Research Consortium; FEC; 5FU/epirubicin/cyclophosphamide; Pts, patients.
*In combination with ovarian suppression in premenopausal patients.

tentially be related to different PTEN assays and cutoff values.[59] Low levels of PTEN, but not necessarily complete loss, can activate the PI3K pathway and reduce treatment efficacy.[58] Preclinical studies suggest that the addition of PI3K/mTOR/AKT inhibitors to anti-HER2 treatment can overcome resistance in tumors with *PIK3CA* mutations,[53,54] a strategy currently being investigated in the clinic.

ESTROGEN RECEPTOR

About half of HER2-positive breast cancer tumors also express ER. The ER and the HER pathways, via a complex bidirectional cross talk, positively and negatively regulate each other,[18,60] so that one pathway can become the escape route to therapy targeted against the other pathway. Indeed, multiple preclinical studies using various HER2-positive breast cancer models have demonstrated the role of ER and its signaling in evading HER2 inhibition and promoting resistance. In ER-positive/HER2-positive breast cancer cells, it has been shown that pre-existing or restored ER levels and/or activity can mediate de novo or acquired resistance to potent anti-HER2 therapy.[27,61] In these resistant cells with sustained HER2 inhibition, ER and its downstream antiapoptotic protein Bcl2 provide key alternative survival stimuli, which in turn sensitize the cells to anti-ER therapies.[61] A study using specimens from a neoadjuvant trial with lapatinib[62] demonstrated a parallel increase in ER and Bcl2 levels after lapatinib treatment.[26] Finally, several studies using ER-positive/HER2-positive xenograft models further showed that a concomitant blockade of ER was crucial to eradicate these aggressive tumors with potent anti-HER2 drug combinations.[37,36,61]

Substantial clinical evidence also supports ER pathway as a mechanism to escape HER2 inhibition.[63-65] Table 4 further shows this important and intriguing finding that was seen consistently across all neoadjuvant trials with dual inhibitors. ER-positive tumors achieved a lower pCR rate than ER-negative tumors. Importantly, among those trials, only the TBCRC 006 trial (trastuzumab plus lapatinib with no chemotherapy) added concurrent endocrine therapy if tumors were ER-positive.[49]

Collectively, the experimental and clinical findings suggest that ER may act as an escape pathway for these tumors, and that concomitant inhibition of ER along with potent anti-HER2 therapy and chemotherapy may abrogate that difference. This concept is currently being tested in the NSABP-B52 trial.

In conclusion, the HER2 pathway represents an attractive therapeutic target that has been successfully attacked in clinic and has resulted in large and meaningful improvements in patient outcomes. However, treatment resistance remains a problem, and can be mediated by several mechanisms. Deciphering these resistance mechanisms is necessary to better tailor therapy to individual patient tumors, optimize patient outcomes, and avoid unnecessary toxicity and cost.

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Combating Acquired Resistance to Tyrosine Kinase Inhibitors in Lung Cancer

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OVERVIEW

The prospective identification and therapeutic targeting of oncogenic tyrosine kinases with tyrosine kinase inhibitors (TKIs) has revolutionized the treatment for patients with non–small cell lung cancer (NSCLC). TKI therapy frequently induces dramatic clinical responses in molecularly defined cohorts of patients with lung cancer, paving the way for the implementation of precision medicine. Unfortunately, acquired resistance, defined as tumor progression after initial response, seems to be an inevitable consequence of this treatment approach. This brief review will provide an overview of the complex and heterogeneous problem of acquired resistance to TKI therapy in NSCLC, with a focus on *EGFR*-mutant and *ALK*-rearranged NSCLC. In vitro models of TKI resistance and analysis of tumor biopsy samples at the time of disease progression have generated breakthroughs in our understanding of the spectrum of mechanisms by which a tumor can thwart TKI therapy and have provided an important rationale for the development of novel approaches to delay or overcome resistance. Numerous ongoing clinical trials implement strategies, including novel, more potent TKIs and rational combinations of targeted therapies, some of which have already proven effective in surmounting therapeutic resistance.

Therapeutic targeting of oncogenes has emerged as a preeminent treatment paradigm for patients with non–small cell lung cancer (NSCLC). Beginning in 2004 with the initial identification of epidermal growth factor receptor (*EGFR*) mutations in a subset of lung adenocarcinomas,[1-3] molecular profiling of lung cancer, particularly lung adenocarcinoma, has evolved into a complex spectrum of clinically relevant and therapeutically actionable genomic alterations. These alterations occur at varying frequencies and, at present, have varying levels of clinical evidence to support the use of targeted inhibitors in each setting. To date, the most well-described molecular cohorts of NSCLC are those defined by the presence of *EGFR* mutations and *ALK* rearrangements. Treatment for patients with *EGFR*-mutant and *ALK*-rearranged NSCLC with specific tyrosine kinase inhibitors (TKIs) that target the EGFR and ALK tyrosine kinases, respectively, has led to remarkable clinical responses, including often-dramatic tumor shrinkage and increased progression-free survival (PFS) compared with standard cytotoxic chemotherapy.[4-10]

Unfortunately, despite the exciting results, virtually every patient who receives TKI therapy and has an antitumor response will eventually experience disease progression. This tumor relapse while the patient is still receiving drug therapy is called acquired resistance and typically occurs within 1 to 2 years after the initiation of the TKI.[4-8,11,12] The development of drug resistance remains a major limitation to the successful treatment for patients with advanced NSCLC. Therefore, numerous preclinical and clinical studies have been directed at identifying and understanding on a mechanistic level the tumor-specific factors that lead to acquired resistance in NSCLC. Given the complexity of the topic, we will specifically focus in this review on *EGFR*-mutant and *ALK*-rearranged NSCLC as paradigms for the use of targeted therapies and the battle to overcome acquired TKI resistance in this disease.

EGFR-MUTANT NSCLC

EGFR is the gene that encodes for the EGFR tyrosine kinase. EGFR propagates growth and survival signals through several downstream pathways within the cell, including the RAS-RAF-MEK-ERK (mitogen-activated protein [MAP] kinase) and the phosphoinositide 3-kinase (PI3K)–AKT–mammalian target of rapamycin (mTOR) pathways. In NSCLC, *EGFR* mutations are typically detected in exons 18 to 21, which encode part of the *EGFR* tyrosine kinase domain. Approximately 90% of these mutations are small in-frame deletions in exon 19 or point mutations in exon 21 (L858R).[13] These mutations activate EGFR kinase activity and are typically detected in lung adenocarcinomas with a frequency of approximately 10% of patients with NSCLC in the United States and of approximately 35% in Asia.[1-3]

EGFR mutations confer sensitivity to and are strong predictors of efficacy for the EGFR TKIs. Several classes of EGFR

TKIs have been tested in tumors that harbor activating *EGFR* mutations, including the first-generation drugs erlotinib and gefitinib and the second-generation drugs, afatinib, dacomitinib, and neratinib. Several randomized, phase III studies have now demonstrated that patients with *EGFR*-mutant tumors (particularly those with the exon 19 deletion and L858R mutations) display an approximately 60% to 70% radiographic response rate (RR) and a PFS of approximately 10 to 13 months with erlotinib, gefitinib, or afatinib therapy.[4-8,14,15] These treatment outcomes are superior to those obtained with standard platinum-based chemotherapy in the same patient population. Therefore, EGFR TKIs are now recommended as first-line therapy for patients with *EGFR*-mutant lung cancer. In the United States, erlotinib and afatinib are both approved by the U.S. Food and Drug Administration (FDA) as first-line therapies for patients with *EGFR*-mutant lung cancer.

ACQUIRED RESISTANCE TO EGFR TKI THERAPY

Acquired resistance to EGFR TKIs is a complex and heterogeneous phenomenon, with multiple potential mechanisms whereby the tumor evades the anti-EGFR– directed therapy. However, the end result for each potential mechanism is sustained signaling through downstream pathways, such as the MAP kinase and PI3K-AKT-mTOR pathways, which prop-

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KEY POINTS

- The identification of clinically relevant molecular cohorts of patients with non−small cell lung cancer (NSCLC), defined by the presence of actionable genomic alterations, has revolutionized the care of patients with this disease.
- Treatment for patients whose lung tumors harbor specific oncogenic mutations often results in dramatic response to targeted therapies, such as tyrosine kinase inhibitors (TKIs). This is best exemplified by *EGFR*-mutant and *ALK*-rearranged NSCLCs treated with *EGFR* TKIs and *ALK* TKIs, respectively.
- Resistance to TKI therapy appears to be an inevitable consequence of this treatment approach. Resistance can be either primary (de novo) or acquired. Specifically, acquired resistance is defined by tumor growth after initial tumor regression while the patient is still receiving the TKI therapy.
- Mechanisms of acquired resistance include drug target gene modification (amplification, second-site mutations), activation of bypass tracks, which serve as compensatory signaling loops, and/or histologic transformation.
- Rebiopsy at the time of acquired resistance is essential for understanding the specific mechanism(s) of resistance at play in the tumor and for directing the patient to the most appropriate line of therapy. Several strategies to overcome acquired resistance, including novel, more potent inhibitors and rational combinations of targeted inhibitors, have already proven successful in clinical trials.

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agate progrowth and prosurvival signals within the tumor. Numerous in vitro studies modeling EGFR TKI resistance in *EGFR*-mutant lung cancer cell lines as well as studies of actual patient tumor samples at the time of disease progression during EGFR TKI therapy[16,17] have yielded important insights into the underlying molecular pathogenesis of acquired resistance (Fig. 1). These mechanisms include (1) modification of the target oncogene, particularly the T790M second-site mutation, (2) upregulation of parallel signaling pathways, such as MET or HER2, to circumvent the inhibited EGFR, and (3) histologic transformation, such as epithelial to mesenchymal transition (EMT) or small cell transformation. Overall, a thorough understanding of the mechanistic basis for acquired resistance is paramount for developing strategies to delay or overcome resistance. Here, we will focus on clinically relevant mechanisms of acquired resistance and proposed strategies to treat progressive disease.

Strategies to Overcome Resistance Mediated by *EGFR* Target Modification

Genomic alterations in the drug target, such as amplification and/or second-site mutations, have been shown to occur as a common mechanism of resistance in many oncogene-driven cancers treated with kinase inhibitor therapy. For example, second-site mutations within the target oncogene have been described for *BCR-ABL* in chronic myeloid leukemia,[18] *EGFR* in NSCLC,[19,20] *ALK* in NSCLC,[21,22] and *ROS1* in NSCLC.[23] In the case of *EGFR*-mutant NSCLC, the most common second-site mutation involves substitution of a methionine in place of a threonine at position 790 (T790M) in the EGFR kinase domain. This T790M gatekeeper mutation is the most common target-specific alteration; it is identified in approximately 50% of patients with acquired resistance to the EGFR TKIs erlotinib and gefitinib.[19,20] The T790M mutation is thought to confer TKI resistance through steric hindrance that interferes with drug binding and/or through alterations in the ATP affinity of the EGFR kinase.[24] Several other second-site mutations within the EGFR kinase domain also have conferred resistance to EGFR TKI therapy, though these mutations appear to occur at a much lower frequency.[25]

In the case of T790M-mediated resistance, one potential strategy to overcome resistance is through the development of novel EGFR inhibitors with increased potency. Erlotinib and gefitinib are first-generation EGFR TKIs that were designed against wild-type EGFR and that reversibly bind to the EGFR kinase domain. Second-generation inhibitors, such as afatinib, neratinib, and dacomitinib, irreversibly bind to the EGFR kinase domain and have activity against other EGFR (ErbB1) family members, including HER2 (ErbB2), HER2 (ErbB3), and/or HER4 (ErbB4). The initial hypothesis was that these second-generation inhibitors would be able to overcome the T790M mutation. Indeed, preclinical data in cell line models did show that the irreversible inhibitors can overcome T790M in vitro.[26-28]

Although the second-generation EGFR/HER2 TKI afatinib is FDA approved for first-line therapy in *EGFR*-mutant NSCLC,[8] this agent has not yet proven to be a promising ther-

FIGURE 1. Mechanisms of Acquired Resistance to First- and Second-Generation EGFR TKIs in EGFR-Mutant NSCLC

Resistance can be mediated by *EGFR* target modifications, most commonly the *EGFR* T790M second-site mutation, through bypass signaling pathways that circumvent the inhibited driver oncogene (*EGFR*) and through histologic transformation (in this case, change in histology from NSCLC to SCLC). Potential strategies to overcome resistance are noted in the white boxes.
Abbreviations: EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

apy in the setting of acquired resistance to first-generation EGFR TKIs, such as erlotinib and afatinib, despite the in vitro studies that suggest that afatinib can overcome T790M. In the phase III LUX-lung 1 study, patients with advanced NSCLC who had previously been treated with erlotinib or gefitinib for at least 12 weeks were randomly assigned to receive afatinib or placebo. Molecular selection for *EGFR* mutation was not required for entrance into the study, and the molecular mechanism(s) underlying the patient's progressive disease during treatment with erlotinib or gefitinib were unknown. The RR and PFS were superior with afatinib, but the study did not meet its primary endpoint of improved overall survival in all study participants or in the subset of patients with known *EGFR*-mutant lung cancer.[29] Likewise, there were no responses in patients with known T790M in clinical trials of other second-generation EGFR TKIs, including neratinib[30] and dacomitinib.[31]

More recently, there has been tremendous excitement surrounding the clinical development of third-generation, mutant-specific EGFR inhibitors. These third-generation EGFR TKIs are irreversible inhibitors, analogous to the second-generation EGFR TKIs; however, they have higher specificity for mutant EGFR (including T790M) than wild-type EGFR. Several agents, including AZD9291, rociletinib (CO-1686), HM61713, ASP8273, and EGF816, are in this class. Of these agents, the mutant-specific EGFR TKIs with the most clinical data reported to date are AZD9291 and rociletinib (CO-1686). Both AZD9291 and rociletinib have activity against EGFR activating mutations (e.g., L858R, exon 19

deletion) and EGFR resistance mutations (e.g., T790M), with little inhibition of wild-type EGFR.[32,33]

Results of a phase I study of AZD9291, which included both the dose-escalation and dose-expansion cohorts, were presented at the 2014 Congress of the European Society for Medical Oncology.[34] Among all evaluable patients, the overall RR in the T790M-positive cohort was 61% (78/127 patients) and the PFS was 9.6 months. In the T790M-negative cohort, the overall RR was 21% (13/61 patients) and the PFS was 2.8 months. The most common adverse events were diarrhea (39%), rash (36%), and nausea (18%), most of which were mild. Overall, AZD9291 appears to be well tolerated, and dose reductions were infrequently needed in the study population.

Analogously, promising results were reported for the phase I/II trial of rociletinib (CO-1686). In the TIGER-X study, two formulations and multiple doses/schedules of rociletinib were evaluated.[35] Data from 56 T790M-positive patients who were treated with rociletinib at the recommended phase II dose of 625 mg twice a day (30 patients) and the step-down dose of 500 mg twice a day (26 patients) indicated an overall RR of 67% in the 27 patients who had evaluable disease. The median PFS was 10.4 months. CO-1686 is well tolerated; hyperglycemia was a frequent adverse event (32%, all grades; 14%, grades 3 to 4).

Numerous other mutant-specific EGFR inhibitors, including HM61713 (NCT01588145), ASP8273 (NCT02192697, NCT02113813), and EGF816 (NCT02108964), are being evaluated in clinical trials. Overall, these mutant-specific

EGFR TKIs appear to be the most effective therapeutic strategy tested to date to overcome T790M-mediated acquired resistance to erlotinib, gefitinib, and afatinib. In fact, both AZD9291 and rociletinib received FDA breakthrough status in 2014.

Despite the excitement surrounding the shown efficacy of mutant-specific EGFR TKIs in T790M-positive tumors, there still remains a large cohort (40% to 50%) of patients with T790M-negative tumors who have developed acquired resistance to erlotinib, gefitinib, or afatinib. One potential strategy that has been postulated for this cohort includes a combination of the EGFR monoclonal antibody cetuximab with afatinib in patients with acquired resistance. This combination, which dually targets *EGFR*, has been studied preclinically[36] and in phase I clinical trials.[37] Among the 126 patients treated with this combination, the objective RR was 29% and was comparable in patients with T790M-positive and T790M-negative tumors (32% vs. 25%; p = 0.341). The median PFS was 4.7 months. Adverse events included expected toxicities of *EGFR* inhibitors, such as rash, diarrhea, and fatigue. Therapy-related grades 3 and 4 adverse events occurred in 44% and 2% of patients, respectively. Studies of afatinib and cetuximab in the first-line setting and at the time of acquired resistance are being planned.

Strategies to Overcome Resistance Mediated by Bypass Signaling Pathways

The majority of focus and attention with respect to acquired resistance to EGFR TKIs has centered on overcoming resistance mediated by the T790M mutation. However, several recent reports have described alternative ways in which a tumor may circumvent inhibited *EGFR*, specifically through activation of collateral signaling networks that can transmit the same downstream progrowth and prosurvival effects within the tumor. Therapeutic strategies aimed at overcoming resistance mediated by this bypass signaling are typically devised to provide continuous inhibition of the driver oncogene (e.g., *EGFR*) while also coinhibiting the compensatory signaling loops that circumvent the inhibited driver. Activation of several different receptor tyrosine kinases, including MET,[16,17] HER2,[38] HER3,[39] insulin-like growth factor 1 receptor (IGF-1R),[40] fibroblast growth factor receptor 1 (FGFR1),[41] and AXL.[42] In addition, activation of the MAP kinase pathway can drive EGFR TKI resistance in vitro and in vivo.[43] The MAP kinase pathway may be activated in this context by virtue of mutations in *BRAF*, a component of the MAP kinase signaling cascade, as well as through reduced expression of neurofibromin, a RAS GTPase-activating protein encoded by the *NF1* gene, which functions as a negative regulator of RAS.[44] Finally, activation of the PI3K-AKT-mTOR pathway, by virtue of *PIK3ca* mutations, can drive resistance to erlotinib and gefitinib.[17]

Numerous clinical trials have been designed to test rational drug combinations that may overcome therapeutic resistance by targeting bypass signaling pathways. Unfortunately, results to date have been somewhat disappointing. (For a review, see Yu et al.[45])

Strategies to Overcome Resistance Mediated by Histologic Transformation

Changes in tumor histology, including EMT and transformation to small cell lung cancer (SCLC), have been documented at the time of acquired resistance to EGFR TKIs.[16,17] The molecular mechanisms initiating these phenotypic changes have not been clearly elucidated to date. In the fraction of patients with EGFR TKI resistance driven by SCLC transformation (3% to 14%), the original *EGFR* mutation is retained. These patients may benefit from treatment with standard platinum-based chemotherapy regimens used in the standard management for SCLC.[46,47]

ALK-REARRANGED NSCLC

ALK is the gene that encodes for the anaplastic lymphoma kinase (ALK). ALK is a receptor tyrosine kinase that is normally expressed in the developing nervous system[48]; however, genomic alterations in *ALK*—including *ALK* amplification, activating point mutations in the *ALK* kinase domain, and *ALK* chromosomal rearrangements—are found in a wide variety of malignancies.[49] In NSCLC, *ALK* is activated through chromosomal rearrangements, most commonly *EML4-ALK*, which is a fusion between the echinoderm microtubule-associated protein-like 4 gene *EML4* and *ALK*, both on chromosome 2. Analogous to EGFR, ALK fusion proteins signal downstream through the MAP kinase and the PI3K-AKT-mTOR pathways. *ALK* rearrangements are typically detected in lung adenocarcinoma and occur at a frequency of approximately 3% to 7%.[11,50]

Several large clinical trials have shown now that patients who have advanced NSCLC and harbor *ALK* rearrangements derive clinical benefits from treatment with ALK TKI therapy. Crizotinib is the first-in-class ALK TKI to be tested in this patient population. Of note, in addition to ALK, crizotinib also targets MET and ROS1. In the phase I, first-in-man study (PROFILE 1005) of crizotinib in patients who have advanced NSCLC and harbor an *ALK* rearrangement, the objective RR was 60.8% (87/143 patients), and the median PFS was 9.7 months.[11,12] On the basis of the high RRs documented in this study, crizotinib was granted FDA approval in 2011 for the treatment of advanced, *ALK*-rearranged NSCLC. Crizotinib also has been studied in randomized, phase III trials. In PROFILE 1007, crizotinib was compared with single-agent chemotherapy (pemetrexed or docetaxel) in patients with *ALK*-rearranged NSCLC who had experienced disease progression after first-line platinum-based chemotherapy. Crizotinib therapy resulted in higher RRs (65% with crizotinib vs. 20% with chemotherapy) and a significantly longer PFS (7.7 months with crizotinib vs. 3.0 months with chemotherapy).[9] There was no difference in overall survival between the groups (20.3 months with crizotinib vs. 22.8 months with chemotherapy), likely because of significant crossover of patients from the chemotherapy arm at the time of disease progression. In the PROFILE 1014 study, crizotinib was evaluated in the first-line setting versus chemotherapy (cisplatin or carboplatin plus pemetrexed) in

343 patients who had advanced *ALK*-rearranged NSCLC.[10] The objective RR was 74% with crizotinib versus 45% with chemotherapy, and the PFS was significantly longer (10.9 months with crizotinib vs. 7.0 months with chemotherapy). The median overall survival was not reached in either group. Therefore, crizotinib is now recommended as first-line therapy for patients who have *ALK*-rearranged lung cancer.

ACQUIRED RESISTANCE TO ALK TKI THERAPY

Analogous to *EGFR*-mutant lung cancer treated with EGFR TKI therapy, acquired resistance to the ALK TKI therapy remains a barrier to the most effective management of this disease. Also analogous to EGFR, acquired resistance to ALK inhibition appears to be a complex and heterogeneous phenomenon that can be mediated through modification of the target oncogene and upregulation of parallel signaling pathways to circumvent the inhibited ALK fusion protein. Acquired resistance to ALK TKI therapy, particularly crizotinib, has been the focus of intense basic science and clinical research (Fig. 2). Target gene modification, including *ALK* amplification and mutation within the *ALK* kinase domain, have been described in both preclinical models and patient tumor samples at the time of disease progression during crizotinib therapy.[21,22,51] Unlike *EGFR*, for which T790M is the predominant mutation found in 50% to 60% of patients with EGFR TKI resistance, only approximately one-third or fewer of patients with crizotinib-resistant tumors harbor an *ALK* kinase domain mutation, and there are numerous mutations that can drive resistance. The two most common mutations described to date are L1196M, which is at the gatekeeper position and is analogous to *EGFR* T790M, and G1269A—

G1269 is the residue immediately before the conserved *DFG* activation motif in the kinase domain.[21,22] Other *ALK* kinase domain mutations that can drive resistance include T1151ins, L1152R, C1156Y, I1171T, F1174L, G1202R, and S1206Y.[21,22,52-54] Interestingly, these different mutations can confer a variable degree of crizotinib resistance in vitro.[21] In addition, to underscore the heterogeneity of crizotinib resistance, the C1156Y and L1196M *ALK* mutations were both found at different tumor sites within the same patient at the time of crizotinib resistance.[52]

Activation of alternative signaling pathways that can bypass the drug-inhibited ALK fusion protein also has been described as a mechanism of crizotinib resistance. This bypass pathway activation can be driven by both genomic and nongenomic changes. For example, increased EGFR phosphorylation (without *EGFR* mutation or amplification) was observed in four of nine tumor biopsy samples at the time of crizotinib resistance compared with the precrizotinib tumor samples.[21] These clinical data are in accord with what has been described for cell line models of ALK inhibitor resistance.[53,55] In addition, increased IGF-1R phosphorylation was observed in cell culture models of ALK TKI resistance, and this result was mirrored in patient tumor biopsy samples taken at the time of progressive disease.[56] Most recently, Src activation also was found to be a driver of crizotinib resistance.[57] The end result of activation of each of these proteins is continued signaling through redundant downstream pathways, despite the presence of the *ALK* inhibitor.

Genomic mechanisms that can drive ALK TKI resistance include mutations in *KRAS* and *MAP2K1*. A *KRAS* point mutation were found in two of 12 patients who had ALK-positive, crizotinib-resistant tumors.[22] Mutations in

FIGURE 2. Mechanisms of Acquired Resistance to Crizotinib in *ALK*-Rearranged NSCLC
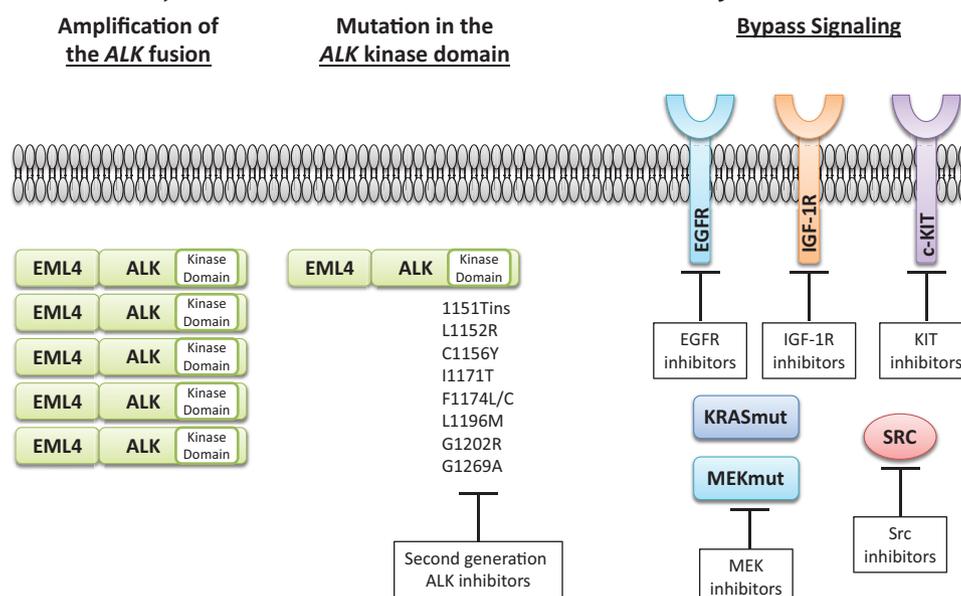
Resistance can be mediated by *ALK* target modifications, including *ALK* amplification and *ALK* kinase domain mutations, and through bypass signaling pathways that circumvent the inhibited driver oncogene (the *ALK* fusion). Potential strategies to overcome resistance are noted in the white boxes.
Abbreviation: NSCLC, non-small cell lung cancer.

MAP2K1, which encodes the protein MEK, were found in one of nine patients who had ALK-positive, crizotinib-resistant tumors.[57] Of note, both of these alterations activate the MAP kinase pathway. Furthermore, amplification of the *cKIT* receptor tyrosine kinase was detected in two of six patient samples with matched pre- and post-crizotinib tumor biopsies.[21]

Strategies to Overcome Resistance Mediated by *ALK* Target Modification

Several second-generation ALK inhibitors are currently being developed clinically. In general, these ALK inhibitors have more on-target efficacy against ALK in vitro than crizotinib and can overcome some of the ALK kinase domain mutations associated with crizotinib resistance.

The most well-studied second-generation ALK inhibitor to date is ceritinib (LDK-378). This agent potently inhibits ALK in vitro in addition to the IGF-1R and insulin receptor. Preclinical studies have shown that ceritinib can overcome the L1196M and G1269A mutations, which appear to be the most common mutations associated with crizotinib resistance.[58] In a phase I study of ceritinib, which included an expansion cohort at the maximum-tolerated dose (750 mg daily), the overall RR was 58%, and the median PFS was 7.0 months among the 114 patients who received at least 400 mg daily.[59] Among the 80 patients who had previously been treated with crizotinib, the RR was 56%, and responses were observed in tumors both with and without detected crizotinib resistance mutations. The most common adverse events reported were elevated liver enzymes and gastrointestinal toxicity (nausea, diarrhea). On the basis of this study, ceritinib was granted accelerated approval by the FDA in April 2014. Finally, ceritinib has documented efficacy against central nervous system (CNS) disease.

Alectinib (CH5424802) is also a second-generation ALK TKI with a distinct chemical structure that can overcome some of the crizotinib resistance mutations, such as the L1196M gatekeeper.[60] In a phase I/II study of this agent in Japan, 43 of 46 patients with ALK inhibitor–naive disease who were treated with the recommended phase II dose achieved an objective response.[61] Alectinib also has been tested in a cohort of patients who experienced progression during treatment with crizotinib or who were intolerant of crizotinib.[62] Of 44 evaluable patients, the objective RR was 55% (24/44 patients). Crizotinib resistance mechanisms were not reported. The CNS RR in patients with CNS metastases at baseline was 52% (11/21 patients). The most common adverse events reported were fatigue, myalgia, and peripheral edema. Alectinib received a breakthrough therapy designation from the FDA in 2013. A randomized, phase III study (ALEX) comparing alectinib to crizotinib in treatment-naive patients with *ALK*-positive lung cancer is ongoing (NCT02075840).

Several other next-generation ALK inhibitors are being studied. Like ceritinib and alectinib, X-396 is more potent against *ALK* in vitro and can overcome crizotinib resistance mutations.[63] A phase I/II trial of this agent is ongoing (NCT01625234); preliminary results indicate that 59% of patients (10/17 patients) achieved a partial response, including patients who had received prior crizotinib.[64] Adverse events were mild and included rash, nausea, vomiting, fatigue, and edema. AP26113, which targets ALK and has activity against the EGFR T790M mutation in vitro, has been tested in a phase I/II study (NCT01449461). The objective RR was 72% and the median PFS was 56 weeks in the 72 patients who had *ALK*-positive NSCLC at the time of data cutoff.[65] In the 65 patients who had received prior crizotinib, the RR was 69%, and the median PFS was 47.3 weeks. CNS responses were documented. Finally, PF-06463922 is a derivative of crizotinib designed to be a more potent ALK/ROS1 inhibitor. This agent also was optimized to overcome some of the pharmacokinetic limitations of crizotinib.[66] A phase I/II trial is ongoing (NCT01970865).

Strategies to Overcome Resistance Mediated by Bypass Signaling Pathways

Such strategies to combat ALK TKI resistance mediated by bypass signaling are only beginning to emerge. Possible rational-combination therapies that have been postulated include an ALK inhibitor plus either an EGFR inhibitor, IGF-1R inhibitor, Src inhibitor, or MEK inhibitor, based on the studies described above. It is also worth noting that ALK inhibitors have been tested in combination with heat shock 90 (HSP90) inhibitors. ALK fusions are known HSP90 client proteins, and in vitro studies demonstrate the efficacy of HSP90 inhibitors in both ALK TKI–sensitive and ALK TKI–resistant models.[67] Furthermore, clinical responses have been documented in patients with *ALK*-positive lung cancer, both in the crizotinib-naive and -resistant states.[67,68] The combination inhibition of ALK plus HSP90 is being evaluated in clinical trials (NCT01579994, NCT01712217, NCT01772797).

CONCLUSIONS

The identification and prospective targeting of oncogenic driver mutations have revolutionized the care of patients who have NSCLC. However, therapeutic resistance remains a significant barrier to the successful management of this disease. Using the two most well-established molecular cohorts of NSCLC, those defined by *EGFR* mutations and *ALK* rearrangements, we have reviewed the molecular mechanisms of acquired resistance and the strategies to overcome resistance. The development of more potent and more selective second- and third-generation oncogenic kinase inhibitors appears to be the strategy with the most momentum and the most documented clinical success to date in both of these cohorts of patients with lung cancer.

However, there are several challenges to address and opportunities to explore moving forward, including:

- How do we effectively address the heterogeneity of resistance mechanisms between different individuals and even in one individual patient? Will multiple biopsies at different sites of disease be necessary, or fea-

sible? Will blood-based markers, such as circulating free DNA, become a way for clinicians to adequately assess resistance mechanisms?

- How do we design and implement novel clinical trials that take into consideration the rapid pace of scientific discovery and the demand to bring more effective therapies into the forefront of care? Furthermore, how do we design these trials to encompass systematic analysis of biomarkers that are found in increasingly smaller percentages of patients? Cooperative group trials, such as the NCI ALK Master Protocol, which is currently being developed, will certainly assist in achieving this design goal.

- What other effective combination therapies can be devised to tackle the problem of TKI resistance? Will cotreatment with different classes of drugs, such as TKIs and immune checkpoint inhibitors, be effective in overcoming resistance? How should these agents be dosed: simultaneously or sequentially?

- Finally, how can cutting-edge studies of TKI resistance in NSCLC be translated to other malignancies? Many of the current and emerging therapeutic targets in NSCLC, such as *ALK, ROS1,* and *RET,* also are found in other malignancies. To more broadly tackle and surmount the problem of acquired resistance, studies in NSCLC, we hope, can be used to inform management in distinct tumor types that harbor these same targets.

Overall, a thorough understanding of the mechanistic basis for acquired resistance and the development of innovative therapeutic strategies to overcome resistance are paramount to most effectively combat resistance and, therefore, to improve the care of patients who have lung cancer.

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Disclosures of Potential Conflicts of Interest

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DEVELOPMENTAL THERAPEUTICS AND TRANSLATIONAL RESEARCH

Precision Medicine through Molecular Profiling: Are We There Yet?

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Clinical Tumor Sequencing: Opportunities and Challenges for Precision Cancer Medicine

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OVERVIEW

Advances in tumor genome sequencing have enabled discovery of actionable alterations leading to novel therapies. Currently, there are approved targeted therapies across various tumors that can be matched to genomic alterations, such as point mutations, gene amplification, and translocations. Tools to detect these genomic alterations have emerged as a result of decreasing costs and improved throughput enabled by next-generation sequencing (NGS) technologies. NGS has been successfully utilized for developing biomarkers to assess susceptibility, diagnosis, prognosis, and treatment of cancers. However, clinical application presents some potential challenges in terms of tumor specimen acquisition, analysis, privacy, interpretation, and drug development in rare cancer subsets. Although whole-genome sequencing offers the most complete strategy for tumor analysis, its present utility in clinical care is limited. Consequently, targeted gene capture panels are more commonly employed by academic institutions and commercial vendors for clinical grade cancer genomic testing to assess molecular eligibility for matching therapies, whereas whole-exome and transcriptome (RNASeq) sequencing are being utilized for discovery research. This review discusses the strategies, clinical challenges, and opportunities associated with the application of cancer genomic testing for precision cancer medicine.

Genomic sequencing technologies have enabled identification of actionable targets (e.g., *BRAF* in melanoma, *EGFR* in lung cancer) thus facilitating treatment selection beyond what is offered by conventional histopathologic methods (Fig. 1). Although NGS has helped identify genomic alterations and uncover novel targets for therapies, there are several barriers for translating this into clinical practice, such as informed consent, choosing a scalable cost-effective testing strategy, turnaround time, and clinical interpretation of results. Several pilot studies have addressed some of these hurdles and demonstrated the feasibility of offering genomic testing for patients with advanced cancer within a clinically relevant time frame and interpreting the results to facilitate new treatment options for patients.[1-6] Today, cancer genomic testing has become more widely available in academic cancer centers and commercial testing labs.

Although whole-genome, whole-exome, and whole-transcriptome sequencing offer an unbiased approach and opportunities for discovery, their immediate effect on clinical decision making is limited, as only a fraction of cancer genes are well characterized in terms of biology and therapeutic relevance. Further, these unbiased sequencing approaches remain expensive and time consuming and are burdensome for computational analysis. All of these limitations make these approaches less amenable to meet standards required for clinical testing, such as Clinical Laboratory Improvement Amendments (CLIA) and College of American Pathology certification. Instead, many academic cancer centers and commercial testing labs have developed focused cancer gene panels ranging from 25 to 400 genes. These cancer gene panels are more cost-effective, have faster turnaround times, and are more scalable for clinical grade testing (Sidebar 1). As an example, Foundation Medicine offers a targeted approach for the entire coding sequence of 315 cancer-related genes plus selected introns from 28 genes often rearranged in solid tumors.[7] Caris provides an assay that combines immunohistochemistry, fluorescence in situ hybridization (FISH), and NGS for selected hotspot mutations involving select exons. However, ARUP Labs offers a targeted DNA sequencing assay for solid tumors for hotspot mutations in 48 genes.

Although genomic tumor testing has become available for patients and oncologists, there are several limitations to consider in practice including specimen quality, distinguishing driver and passenger mutations, tumor heterogeneity, and incidental germ-line mutations. Genomic testing and interpretation can be limited by tumor content and the quality of small, formalin-fixed tumor samples. Although formalin-fixed paraffin embedded (FFPE) samples may be subject to degradation complicating sequencing, strategies that accommodate FFPE samples have been successfully developed.[8,9] At times, there may be a need for repeat or fresh frozen tumor

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FIGURE 1. Potential Applications of Cancer Genomic Testing

Potential Applications of Cancer Genomic Testing

Diagnosis	Tissue-of-origin Testing in Cancer of Unknown Primary
Prognosis	BRAF Mutations and Risk of Relapse
Screening	Plasma miRNA Screening Trial for Cancer
Predictive	New Treatments Opportunities for Metastatic Cancer
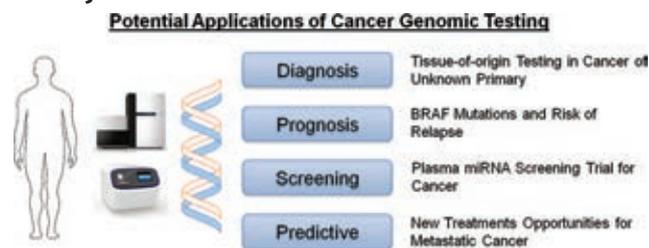
Cancer genomic sequencing assays can aid clinical decision making with potential implications for diagnosis, prognosis, and treatment. Several assays are available to aid in identifying tissue-of-origin in cancer of unknown primary, which may lead to identification of potential favorable subsets and their appropriate treatment options. For patients with metastatic or refractory cancer, multiple testing strategies are available to identify genomic alterations that may provide molecular eligibility for novel targeted therapies in clinical trials.

biopsies as these may provide better quality for sequencing and can support specialized research assays. Although cancer gene panels focus on identification of potentially targetable driver mutations that provide a selective growth advantage for tumors, it is often hard to discern the role of passenger or bystander mutations. Also, pretreatment of tumors with cytotoxic therapies can often lead to increased genomic instability and alterations, making interpretation of tumor evolution and heterogeneity an arduous task.[10] Gerlinger et al highlighted the challenges associated with tumor heterogeneity and the potential limitations of a single biopsy, as different sites of metastases may have different tumor subclones and mutations.[11] However, it is expected that the dominant mutations exist as "trunk" mutations and would be the priority target for therapy. Finally, to aid in distinguishing driver and passenger mutations, it may also be helpful to have tumor and normal genomic testing by assessing germ-line DNA obtained from blood or buccal smears to allow distinction of somatic variants from germ line. However, germ-line sequencing also presents issues including the need for informed consent, counseling, expertise to interpret germ-line

KEY POINTS

- Targeted gene capture panels are more commonly employed in clinical practice because of reduced costs and faster turnaround time.
- In addition to gene expression and fusions, RNA sequencing also facilitates the profiling of noncoding RNAs.
- Germ-line DNA testing can help distinguish somatic mutations from inherited variants but has logistic challenges.
- Tumor heterogeneity, discerning drivers from passenger mutations, and acquired resistance are potential challenges with developing genomics-driven targeted therapies.
- Genomic tumor sequencing can explain how some patients develop exceptional response to therapies and help further development of a therapy.

SIDEBAR 1. Pros and Cons for In-House versus Outsourced Cancer Genomic Testing

- Customizable gene panel content
- Access to quality metrics and variant frequencies
- Cost-effective in the long run
- Integration of reports into electronic health records
- Unified platform for clinical use and discovery

findings, and disclosure.[12] This requires substantial resources and time and limits the broader use of germ-line tissue in oncology practices. Consequently, most commercial vendors offer tumor only testing.

STRATEGIES FOR MOLECULAR PROFILING

Whole-genome sequencing offers the most comprehensive strategy for tumor genomic analysis; however, it is currently limited in its clinical applicability because of cost and turnaround time for sequencing and analysis. Therefore, strategies that incorporate targeted gene sequencing are preferred for clinical applications, reducing cost, and offering a faster turnaround time. Nonetheless, since these panels test for select genes, they may miss opportunities for discovery that are afforded by other intermediate approaches, such as whole exome and transcriptome sequencing, which focuses on the expressed components of the genome.

Targeted DNA Sequencing

Although comprehensive approaches are necessary to achieve a complete genomic characterization of a patient's tumor, many clinical laboratories have employed targeted DNA sequencing approaches as a practical alternative.[7,13-15] Targeted sequencing of hundreds of genes selected according to their relevance to cancer enables cheaper and higher-throughput molecular profiling of patients' tumors and incurs more manageable computational requirements with regard to data storage and analysis. Further, the deeper sequence coverage afforded by targeted sequencing can result in increased detection sensitivity for mutations in heterogeneous or low purity tumors. Consequently, large numbers of patients can be screened for genomic alterations, predicting response to approved and investigational targeted therapies, with high confidence that all clinically significant mutations will be detected.

Several products are available for capturing and sequencing genomic regions of interest—all compatible with FFPE tumor tissue. Target capture methods fall into two main classes: enrichment by amplification and enrichment by hybridization. Enrichment by amplification, or amplicon capture, relies on a highly multiplexed polymerase chain reaction involving locus-specific primer pairs simultaneously amplifying target regions in the genome. Amplicon capture can produce deep sequence coverage with very little DNA, but it is typically suitable only for a limited number of genes.

Further, amplicon capture methods may not be reliable for the detection of structural alterations such as copy number gains or losses and translocations. Panels based on amplicon capture often target hotspots of recurrent somatic mutations rather than the entire coding sequence of the genes and are typically coupled with benchtop DNA sequencers, such as the Illumina MiSeq and the Ion Torrent Personal Genome Machine. Enrichment by hybridization, or hybridization capture, utilizes synthetic DNA or RNA probes that bind to and enrich for complementary genomic DNA. Hybridization capture usually requires more input DNA than amplicon capture, but it can scale to a larger number of genes (up to the whole exome). Panels based on hybridization capture typically target all coding sequences of all genes and can be coupled with either benchtop or production sequencers, such as the Illumina HiSeq and the Ion Torrent Proton. Importantly, hybridization capture methods enable the accurate detection of copy number alterations and selected structural rearrangements.[16] Both amplicon and hybridization capture methods benefit greatly from the use of sample barcodes, which permit many tumors to be profiled in a single NGS run.

One of the most important decisions in the development of any cancer gene panel is what the content should be. Ideally the test will encompass all genes with "actionable" mutations that may affect a patient's treatment course. Additional genes may be considered if they have demonstrated biologic importance based on preclinical evidence. Custom panels afford the flexibility to target noncoding sequence, such as promoters and regulatory regions in the assay. By capturing introns of recurrently rearranged genes, it is possible to detect genomic breakpoints that produce gene fusions—many of which may be targeted by approved or experimental therapies. Ultimately, decisions about which and how many genes to sequence are best made by individual clinical laboratories according to their anticipated volume of cases, desired turnaround time and cost, and whether matched normal tissue is available for companion analysis.

RNA Sequencing in the Clinic

In addition to targeted DNA sequencing, RNA sequencing (RNAseq) can be supplemented by profiling the cancer transcriptome. RNAseq can provide data on gene expression, mutations, and gene fusions in cancer. Gene fusions have long been recognized as important in the oncogenesis of hematologic malignancies (e.g., *BCR-ABL1* fusion in chronic myeloid leukemia); however, these were not well studied in solid tumors until the advent of NGS. RNASeq can be utilized for detection of novel fusions at a fraction of the cost of whole-genome sequencing. This has resulted in the characterization of novel oncogenic fusions with matching targeted therapies across various tumors (e.g., *ALK, ROS1, RET* fusions in lung cancers).[17,18] Also, RNASeq can detect cryptic or novel translocations or gene fusions in leukemia that are not detectable by standard karyotyping or FISH.[19] Nevertheless, RNAseq sequencing remains expensive and not easily implemented in clinical labs. Therefore, strategies that utilize targeted RNASeq may be preferable for rapid turnaround

and reduced cost.[20] For example, Zheng et al implemented an anchored multiplex RNAseq strategy to detect selected gene fusions in cancer. For sarcomas, Qadir et al demonstrated the feasibility of targeted RNAseq to detect prototypic fusions, which could replace costly FISH assays and facilitate detection of novel fusions.[21] Several commercial and academic entities are developing additional clinical grade RNAseq strategies. Consequently, we anticipate a combination of DNA and RNA sequencing may have synergy as a clinical tumor sequencing strategy, incorporating data on DNA mutations and gene expression.

In addition to gene expression and fusions, RNASeq permits broader profiling of the cancer transcriptome, including detection of noncoding RNAs (ncRNA) such as microRNAs (miRNAs), small interfering RNAs, ribosomal RNAs, small nucleolar RNAs, and long noncoding RNAs. In fact, more than half of the cancer transcriptome consists of ncRNAs.[22] These ncRNAs have been shown to be important in multiple cellular processes, such as gene silencing, DNA replication, and regulation of transcription and translation.[23] Although the majority of these RNAs may not be applicable for clinical use, there is abundant potential for biomarker discovery and development. For example, miRNA profiling has been utilized to develop cancer-specific signatures that could be developed as diagnostic, early screening, prognostic, and treatment predictive biomarkers.[24] A commercially available test has been developed to help classify tissue of origin in patients with cancer of unknown primary. These tissue-of-origin tests assess miRNA signatures that were derived from miRNA profiling 20 to 40 cancer subtypes and can help clinicians identify favorable subsets for cancer of unknown primary that may lead to treatment decisions.[25,26] In another example, Sozzi et al developed a signature of miRNA from plasma of patients with lung cancer, and they are studying whether this test can improve accuracy of screening in combination with CT scans in a prospective screening study for lung cancer.[27] Thus, there is great potential for ncRNA-specific signatures to aid diagnostic dilemmas and potentially identify new treatment options as we learn more about ncRNA biology.

IMPLEMENTATION OF A CLINICAL SEQUENCING WORKFLOW
Challenges and Considerations

When developing clinical sequencing workflows, academic and commercial laboratories must confront many challenges. In contrast to the research setting, where large, high-purity, fresh-frozen tumors can be prioritized for analysis, clinical laboratories must be equipped to analyze specimens of all sizes and qualities. These may include small biopsies, fine-needle aspirates, or FFPE samples that are heterogeneous or admixed with normal tissue. Sequencing protocols must be optimized for low-quality specimens and low-input quantities and still deliver deep coverage sequence data for the reliable detection of mutations with low allele frequency. Further, laboratories must be able to deliver results with a

rapid turnaround time at a reasonable cost. The use of germ-line DNA from blood or healthy tissue as a normal control has major benefits for the analysis and interpretation of somatic mutations, but it creates logistic challenges involving tracking and transporting separate samples from the same patient. As multiple tumor samples from a given patient may occasionally be sequenced to monitor tumor progression and acquired resistance to therapy, flexible workflows are necessary to accommodate longitudinal analysis. Though the nature of these issues may vary for different laboratories depending on their throughput and sequencing platforms, they represent technical challenges common to all clinical laboratories.

Bioinformatics and analysis requirements collectively represent another important challenge in establishing a clinical sequencing workflow. The bioinformatics algorithms and software required to call different classes of genomic alterations (sequence mutations, insertions, deletions, copy number gains and losses, and structural rearrangements) are constantly evolving, and there remains no consensus on the best approach or standardized pipeline. Laboratories performing NGS have the choice of utilizing third-party software for data analysis, which can be costly and limits flexibility, or developing custom pipelines in-house, which requires considerable time and expertise to build and maintain. Either way, a significant informatics infrastructure is needed to manage, store, and archive the data generated by the sequencing instruments and the results produced by bioinformatics pipelines. Access to high-performance computing resources for processing and analyzing sequence data is required. Laboratory information management systems and associated databases are typically also needed to track samples, experiments, and results. For hospitals and clinical laboratories that have not traditionally employed many computational biologists and software engineers, the recruitment and training of bioinformatics staff is challenging yet essential.

Regulatory requirements, including the up-front analytic and clinical validation of assays, must also be met in any clinical sequencing workflow. Clinical laboratories producing results that are returned to patients and used in treatment decisions are subject to legal obligations designed to ensure that tests are reproducible and adhere to high standards of sensitivity and specificity. Such labs, whether commercial or academic, must be compliant with the CLIA, under the oversight of the Centers for Medicare & Medicaid Services. Accordingly, extensive documentation and technical validation of diagnostic assays are a requirement for patient testing and subsequent billing to insurance companies and Medicare. The model that some institutions have adopted wherein large-scale sequencing is performed in research labs, followed by confirmation in CLIA-compliant labs, is unsustainable over the long-term if the costs of NGS cannot be recovered through reimbursement.

To achieve maximum clinical benefit from a diagnostic sequencing assay, results must be reported to clinicians in a clear and easily digestible way, yet with all supporting information necessary to interpret the significance of the collection of genomic alterations that were detected.[28] The interpretation of results is frequently dependent on tumor type and other clinical factors and must be considered in that context. Also, although the goal is to identify actionable driver mutations, clinical sequencing assays typically turn up far more passenger mutations with unclear biologic and clinical significance. This is especially true in tumors with a high background mutation rate because of environmental exposures or abnormalities in DNA mismatch repair. It can be very difficult for a clinician to distinguish between key driver alterations that should affect treatment and passenger mutations with no apparent significance. Many academic cancer centers have created genomic or molecular "tumor boards" to collectively discuss and interpret challenging cases and recommend a course of action that the treating physician can take.[4,29] As this process does not easily scale to accommodate the large number of tumors being sequenced today, groups have attempted to curate and codify biologic and clinical information about mutations into databases that can be queried or utilized to annotate molecular diagnostic reports.[9,30] These "knowledge bases" must be granular enough to account for the fact that different sequence variants in the same gene may have opposite effects, and the same variant in different tumor types may have different clinical consequences. They should also enable the enumeration of clinical trials that might be beneficial to the patient, given their molecular profile. Nevertheless, no knowledge base is comprehensive or will ever include information on all possible alterations that a sequencing assay may reveal. Further, the co-occurrence of multiple driver mutations may have implications that cannot be inferred from the functions or clinical consequences of each individual mutation alone.

With the exception of targeted panels focused on mutational hotspots, germ-line DNA is typically used as a normal control to distinguish somatic mutations from inherited variants. In the absence of germ-line DNA, variants identified from tumor sequencing must be filtered according to databases of common single nucleotide polymorphisms. This can lead to false-positive mutation calls at sites of rare inherited single nucleotide polymorphisms, including cancer susceptibility alleles. The inclusion of germ-line DNA enables somatic mutations to be unambiguously called; yet it also enables the detection of pathogenic variants in the genes that are sequenced. This has considerable ethical and logistic implications. Incidental findings may emerge as a result of tumor sequencing that relate to a patient's inherited susceptibility to cancer or other diseases, with unanticipated yet significant consequences for family members who share these variants.[31,32] At present, tests specifically designed to search for inherited genetic variants typically require that patients sign informed consent and are properly educated of the benefits and risks of the test by a genetic counselor. For laboratories setting up large-volume tumor sequencing initiatives, individual pretest genetic counseling of all patients may be untenable. Computational subtraction of germ-line variants during mutation calling may circumvent the requirement for

TABLE 1. Commercial Targeted DNA Tumor Sequencing

Vendor	Name	No. of Genes	Results	Time
Foundation Medicine	Foundation One	315 (plus introns from 28 genes)	SNVs, CNVs, fusions	12-14 days
Caris Life Sciences	MI Profile	46	Hotspot mutations	14 days
ParadigmDx	PCDx	114	SNVs, CNVs, fusions	4-5 days
ARUP Labs	Solid Tumor Mutation Panel	48	Hotspot mutations	14 days
PathGroup	SmartGenomics	35	Hotspot mutations	7-10 days
Knight Diagnostic Labs	GeneTrails Cancer Gene Panel	38	Hotspot mutations	10-14 days
Life Technologies	Pervenio Lung NGS Assay	25	SNVs, fusions	7 days

Abbreviations: SNV, single nucleotide variation or point mutation; CNV, copy number variation; NGS, next-generation sequencing.

pretest counseling, but it also has the consequence that inherited variants with potential clinical significance are willfully disregarded.[33] Regardless of the circumstances, when an inherited predisposition to cancer (or another disease) is discovered, care must be taken to ensure the privacy and autonomy of patients and their families and to help manage the emotional and psychologic consequence of such a diagnosis.

As discussed above, the sustainability of clinical NGS initiatives depends on reimbursement from insurance companies and Medicare. However, at present, molecular diagnostic testing is only reimbursed in a small number of tumor types where there are approved drugs whose administration depends on a positive or negative test result and where there are clear clinical guidelines mandating the use of molecular testing. Examples include lung adenocarcinoma, colorectal cancer, and melanoma. In other tumor types where comparable guidelines do not exist, more data are needed to determine the clinical utility of NGS-based molecular profiling. As a result, large academic cancer centers are investing considerable philanthropic and other institutional funds into clinical sequencing of nonbillable tumor types. Demonstrating the clinical utility of tumor sequencing across additional cancer types is essential to ensure greater reimbursement and promote broader access to testing outside of the largest centers. A related issue emerges when actionable mutations are detected in unexpected tumor types, and insurance companies are not always willing to reimburse the cost of the drug for an off-label indication. The emergence of molecularly guided clinical trials encompassing multiple tumor types, or "basket" clinical trials, may help some patients in this situation.

In-house versus Outsourcing

With all of these challenges inherent to the establishment of clinical sequencing infrastructure, it is tempting for academic cancer centers and community oncology practices to outsource the entire process to a commercial reference laboratory. For many centers, this may be the best decision given financial, volume, and staffing considerations. However, there are many advantages to setting up these processes in-house that can justify the effort and expense from an institutional perspective (Table 1).

First, developing and validating a tumor sequencing test in-house gives the laboratory ultimate control over the content of the assay. Panels can be designed to include targets of all clinical trials open within the institution as well as genes and noncoding regions suggested by preclinical research studies. Further, as new clinical knowledge emerges and new clinical trials are developed, additional genes and biomarkers can rapidly added. Second, the laboratory and collaborating investigators will have access to all raw data, including sequence quality metrics and mutation allele frequencies, which one would not expect to receive from an outside provider. This can enable the development of custom bioinformatics pipelines to explore additional features of the data such as tumor heterogeneity and clonal evolution, and the reanalysis of data as new tools and algorithms are created. Importantly, data access will also facilitate data mining initiatives through integration of clinical and phenotypic data for the patients whose tumors were sequenced. Third, though the establishment of clinical NGS tests requires a large upfront investment, it may ultimately lead to lower costs than commercial providers will offer, especially for large-volume laboratories. Additionally, as discussed above, institutions can use philanthropic and institutional funds to pay for nonbillable tests that will produce data to possibly justify reimbursement in the future. Fourth, analysis results and molecular reports can be integrated directly with the hospital information systems. This can facilitate rapid reporting, deposition into institutional databases, and the screening and selection of patients for clinical trials. As clinical trials in oncology increasingly require the presence of particular (often rare) genomic alterations, an institutional molecular database can help identify the patients that meet all eligibility criteria and are most likely to benefit from a new drug. Fifth, the same test that is validated and approved for clinical use can also be used to retrospectively analyze archived tumors, such as those obtained from "exceptional responders," for research purposes.[34,35] This allows data from a single platform to be merged and mined with greater power to discover biomarkers that correlate with clinical outcomes and/or response or resistance to therapy. It also provides additional flexibility to further develop and optimize the assay for other types of specimens, such as cell-free DNA from plasma or cerebrospinal fluid.

IMPACT OF CANCER GENOMIC TESTING IN THE CLINIC

Although the availability of cancer genomic testing in the clinic has led to opportunities in oncology such as drug target discovery, it has also led to challenges including how to develop targeted therapies for small populations of patients with rare mutations. For example, in contrast to the frequency of *ERBB2* amplification in breast cancer and *BRAF* mutations in melanoma (20% and 45%, respectively), the majority of actionable genomic alterations revealed by clinical tumor sequencing typically occur at frequencies of 2% to 5%. This has raised several challenges for delivering treatment to patients and developing novel therapies in clinical trials.

For example, cancer genomic sequencing enabled discovery of novel activating somatic point mutations the *ERBB2* gene in patients with breast cancer who were negative for *ERBB2* gene (HER2) amplification, but these mutations are only found in 1% to 2% of patients with breast cancer.[36] In vitro studies demonstrated that these activating mutations conferred resistance to reversible inhibitor lapatinib but were sensitive to neratinib, an irreversible *ERBB2* inhibitor.[36] This has led to a phase II study of neratinib for patients with metastatic *ERBB2*-mutant breast cancer.[2] Although this strategy appears rational for a disease- and mutation-specific trial, moving forward for other uncommon genomic alterations within a single tumor type, typical large randomized phase III trials will not be pragmatic for each disease and each mutation subset. Meanwhile predictive biomarker selection has led to exceptional tumor responses to matching therapies, and phase II trials may provide convincing evidence of clinical activity and benefit.[37-39] The low prevalence of actionable oncogenic mutations has led to the evolution of "basket trials." Unlike a conventional tumor histology–based clinical trial, patient selection is based on a specific genomic alteration and not on tumor type.[40] This is different from BATTLE or I-SPY trials in which adaptive design is utilized to enrich patients into specific molecular cohorts based on initial efficacy results, while restricted to a single tumor type. Presently, basket trial approaches will unlikely lead to regulatory drug approval in a specific tumor type, but they help assess whether all or selected cancer types with specific genomic alterations (e.g., *FGFR, BRAF*) would indeed respond to a matching targeted therapy, and they help consider other endpoints, such as magnitude of response, duration of responses, and the study of novel predictive biomarkers for sensitivity and resistance.[41] Finally, basket trials enable enrollment of multiple tumor types and facilitate patient accrual for both rare cancers and genomic alterations.

In addition to prospective trials, cancer genomic testing may help us understand clinical responses retrospectively based on patients who have exceptional responses to therapy. Iyer et al observed a complete, durable response of more than 2 years in a single patient with metastatic bladder cancer with everolimus treatment on a clinical trial that did not meet its primary endpoint. They performed whole-genome sequencing of the tumor, which revealed a mutation in *TSC1*, a gene involved in the mTOR pathway. They subsequently demonstrated a basis for clinical response to everolimus, an mTOR inhibitor.[34] Similarly, whole-exome sequencing on a patient with metastatic anaplastic thyroid cancer, who had an exceptional response to everolimus, identified a mutation in *TSC2*, a negative regulator of the mTOR pathway.[42] These individual patients highlight an application of genomic sequencing to understand how we can learn from exceptional responders to guide further development of targeted therapies. The National Cancer Institute and academic cancer centers are actively seeking to apply this approach in ongoing clinical trials across the country to guide drug development based on novel predictive biomarkers.

Finally, as we learn to identify the correct genomic alteration that can predict response to a therapy, we must also prospectively consider how cancers become resistant to therapy. Although targeted therapies may lead to remarkable initial responses for patients with selected biomarkers, metastatic cancers inevitably acquire resistance. NGS has been utilized to characterize mechanisms of secondary resistance to identify potential combinatorial therapies that can prevent or delay emergence of resistance. Wagle et al performed NGS in a patient with metastatic melanoma who developed resistance to vemurafenib after showing initial response. They identified an acquired mutation in *MEK1,* conferring resistance to RAF or MEK inhibition.[43] Tumor sequencing has also helped identify resistance mechanisms in long-established therapies, such as estrogen blockade in breast cancer, where ligand-binding domain mutations in *ESR1* (the estrogen receptor) mediate acquired resistance to antihormonal therapy.[44,45] Similarly, whole-exome sequencing has been utilized to study acquired resistance to the recently approved BTK inhibitor ibrutinib in relapsed chronic lymphocytic leukemia and has identified a mutation in *BTK* that limits drug binding.[46]

CONCLUSION

Although the application of clinical tumor sequencing has enabled identification of actionable genomic alterations that could provide molecular eligibility to matching targeted therapies, clinical application and interpretation does have some challenges. Intratumor heterogeneity, discerning drivers from passenger mutations, lack of sustained response, and acquired resistance to targeted therapies are some of the issues that limit the potential of genomics-driven targeted therapies. Further, responses to targeting tend to vary across tumors and within a tumor depending on the treatment context. Biopsies at multiple time points, rational combination therapies, and basket trial designs can help address some of these issues. As oncology is migrating to a more molecularly matched therapy paradigm, a strong collaboration between basic scientists, molecular pathologists, bioinformaticians, and oncologists is paramount in an effort to identify novel cancer therapies that lead to improvement in patient survival.

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Clinical Trials of Precision Medicine through Molecular Profiling: Focus on Breast Cancer

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OVERVIEW

High-throughput technologies of molecular profiling in cancer, such as gene-expression profiling and next-generation sequencing, are expanding our knowledge of the molecular landscapes of several cancer types. This increasing knowledge coupled with the development of several molecularly targeted agents hold the promise for personalized cancer medicine to be fully realized. Moreover, an expanding armamentarium of targeted agents has been approved for the treatment of specific molecular cancer subgroups in different diagnoses. According to this paradigm, treatment selection should be dictated by the specific molecular aberrations found in each patient's tumor. The classical clinical trials paradigm of patients' eligibility being based on clinicopathologic parameters is being abandoned, with current clinical trials enrolling patients on the basis of specific molecular aberrations. New, innovative trial designs have been generated to better tackle the multiple challenges induced by the increasing molecular fragmentation of cancer, namely: (1) longitudinal cohort studies with or without downstream trials, (2) studies assessing the clinical utility of molecular profiling, (3) master or umbrella trials, (4) basket trials, (5) N-of-1 trials, and (6) adaptive design trials. This article provides an overview of the challenges for clinical trials in the era of molecular profiling of cancer. Subsequently, innovative trial designs with respective examples and their potential to expedite efficient clinical development of targeted anticancer agents is discussed.

Personalized medicine is defined by the National Cancer Institute (NCI) as "a form of medicine that uses information about a person's genes, proteins and environment to prevent, diagnose and treat disease."[1] In oncology, this is a dynamically evolving field, with an increasing list of molecular markers from tumor tissue dictating the treatment selection of patients with several cancer diagnoses (Table 1). In the setting of breast cancer, personalized medicine was first exemplified with the introduction of hormone receptor (HR) assessment and the subsequent use of endocrine treatment changing the natural history of HR-positive breast cancer.[2] Interestingly, the first clinical trials demonstrating clinical benefit deriving from the use of tamoxifen in the setting of breast cancer were performed for all cancers, irrespective of HR positivity.[3,4] As a result of the high frequency of this overexpression in breast cancer, efficacy signals were captured even within this unselected patient population.

On the contrary, the success story of trastuzumab for patients with HER2 positivity, defined as protein overexpression and/or gene amplification, used a different route: the respective clinical trials in both metastatic and early-stage disease recruited exclusively patients with HER2-positive breast cancer.[5,6] Subsequent studies assessing other HER2 blocking agents have been conducted within this particular molecular niche of breast cancer, for which four different tar-

geted agents have been approved at present.[7] Other tumor entities provide similar examples of how molecular preselection of patients for study enrolment can accelerate efficient clinical development of molecularly targeted agents. In the case of non–small cell lung cancer (NSCLC), the IPASS (Iressa Pan-Asia Study) study randomly assigned 1,217 unselected patients with previously untreated advanced disease to receive gefitinib or carboplatin/paclitaxel. In the final analysis performed according to epidermal growth factor receptor (EGFR) biomarker status, it was reported that progression-free survival (PFS) was significantly longer with gefitinib for patients whose tumors had both high *EGFR* gene copy number and EGFR mutation (hazard ratio [HR], 0.48; 95% CI, 0.34 to 0.67, p < 0.001) but significantly shorter when high *EGFR* gene copy number was not accompanied by *EGFR* mutation (HR, 3.85; 95% CI, 2.09 to 7.09, p < 0.001).[8] This finding confirmed the previously established knowledge that administration of EGFR-blocking agents should be dictated by the presence of *EGFR* mutations in NSCLC.

In the setting of breast cancer, multiple oncogenic signaling pathways have been identified as promoters of the malignant progression with numerous aberrations, such as mutations and/or copy number variations affecting their molecular components. Such pathways operate in (1) bulk tumor cells, (2) a subset of tumor initiating cells, and/or (3)

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TABLE 1. Molecular Aberrations Defining Administration of Approved Targeted Agents in Different Solid Tumor Diagnoses

Cancer Type	Molecular Target	Aberration	Method of Assessment	Approved Targeted Agent
Breast Cancer	ER	Overexpression	IHC	Tamoxifen
				AIs
				Fulvestrant
	PgR	Overexpression	IHC	Tamoxifen
				AIs
				Fulvestrant
	HER2	Overexpression and/or amplification	IHC	Trastuzumab
				Pertuzumab
			FISH	Lapatinib
				T-DM1
Colorectal Cancer	KRAS*	Mutation	DNA	Cetuximab
				Panitumumab
Gastric Cancer	HER2	Overexpression and/or amplification	IHC	Trastuzumab
			FISH	
GIST	KIT	Mutation	IHC	Imatinib
Melanoma	BRAF	Mutation	DNA	Vemurafenib
				Dabrafenib
Non-Small Cell Lung Cancer	EGFR	Mutation	DNA	Gefitinib
				Erlotinib
	ALK	Rearrangement	FISH	Crizotinib
	RET	Rearrangement	FISH	Vandetanib
	ROS	Rearrangement	FISH	Crizotinib

Abbreviations: AI, aromatase inhibitor; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; ER, estrogen receptor; FISH, fluorescent in situ hybridization; GIST, gastrointestinal stromal tumor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PgR, progesterone receptor; T-DM1, trastuzumab DM1.
*KRAS mutations predict lack of benefit derived from EGFR-blocking agents.

the tumor microenvironment. An expanding arsenal of targeted agents is currently under clinical development, aiming to block specific molecular aberrations[9] ; however, the extended tumor heterogeneity seen poses impediments to their success.[10] The increasing number of targeted agents warranting clinical assessment, coupled with the increasing molecular fragmentation of breast cancer and thus the respective decrease in prevalence of putative predictive biomarkers, render the current clinical trial paradigm inefficient. New study designs are needed to facilitate the successful clinical development of targeted agents within specific molecular niches of breast cancer.[11]

KEY POINTS

- The success stories of trastuzumab and endocrine treatment for patients with HER2-positive and hormone receptor-positive breast cancer exemplify the potential of personalized cancer medicine.
- High-throughput molecular profiling techniques reveal the extensive molecular diversity of breast cancer, leading to an increased molecular fragmentation.
- There is an increasing number of targeted agents that need to be assessed in the setting of breast cancer.
- Clinical assessment of targeted agents within small molecularly defined breast cancer segments poses challenges to the design and conduct of clinical trials.
- New, innovative study designs are being introduced to overcome these challenges.

MOLECULAR PROFILING IN BREAST CANCER

The advent of gene-expression profiling analysis led to the identification of four intrinsic subtypes of breast cancer, associated with different prognostication and sensitivity profiles to treatment,[12] namely: (1) luminal A, being HR-positive with low proliferation rates, (2) luminal B, HR-positive with higher proliferation rates, (3) HER2-like, characterized by amplification of the *ERBB2* gene as well as other genes in the same amplicon, and (4) basal-like, largely showing a triple phenotype with lack of expression of estrogen receptor, progesterone receptor, and HER2. Of note, these subtypes show distinct molecular profiles, as indicated by studies that coupled gene expression profiling with genome copy number analysis.[13,14] Subsequent studies, implementing this powerful technique to larger collections of primary breast tumors, have led to further molecular fragmentation of this common

TABLE 2. Approaches of Next-Generation Sequencing

Approach	Advantages	Disadvantages
Whole-Genome Sequencing	· Potential for identification of previously unrecognized cancer related genes and aberrations · More efficient interrogation of structural variations	· Higher costs · Longer turnaround time · Laborious bioinformatics work · High storage capacity needed · Challenging clinical interpretation/reporting · Low reproducibility of FFPE tumor material analysis
Targeted Sequencing	· Lower costs	· Limited potential for identification of previously unrecognized cancer-related genes
Whole-Exome Sequencing	· Shorter turnaround time	· Reduced capacity to interrogate of structural variations
Targeted Gene Sequencing	· Easier data interpretation · Lower data storage capacity needed · Easier clinical interpretation/reporting · Ready to be used for FFPE	

disease. An integrated analysis of almost 2,000 primary breast cancers combining copy number and gene expression data from the METABRIC (Molecular Taxonomy of Breast Cancer International Consortium) group revealed a total of 10 different subgroups with distinct prognoses.[15] Further molecular classes have been identified within basal-like breast cancerbreast cancer, such as: (1) the claudin-low tumors characterized by a gene expression profile similar to that of mammary stem cells and mesenchymal features,[16] and (2) molecular-apocrine tumors characterized by expression of androgen receptor and consecutive downstream signaling.[17]

More recently, there have been studies employing next-generation or massively parallel sequencing (NGS and MPS, respectively) in breast cancer, expanding further our understanding of the underlying molecular heterogeneity.[18-22] NGS is a powerful molecular profiling tool, deciphering DNA sequences and informing us about a variety of different molecular aberrations, namely nucleotide substitution mutations, insertions and deletions, copy number variations, and structural rearrangements.[23] Importantly, the ability of NGS to quantify the allelic frequency of any mutational event captured enables the reconstruction of the clonal architecture of any given tumor sequenced.[24,25] These studies document the extensive intertumor heterogeneity of breast cancer, as exemplified by the study of Stephens et al, in which among the 100 sequenced breast cancers there were 73 different combination of possibilities of mutated cancer genes.[22] Additionally, a repetitive finding from these studies is that unlike some few commonly mutated cancer genes such as *TP53* and *PIK3CA*, most of the gene mutations are seen in less than 10% of the cases that are sequenced.[26,27] Last, the determination of the allelic frequencies indicates than not all mutated genes reported are of clonal nature, since some of them are found in a subclonal population of cancer cells.

There has been an increasing availability of NGS techniques to many investigators thanks to a steep decrease in the financial costs involved that surpassed to what Moore's law foresaw.[28] Currently, different applications of NGS are under use that could be summarized as follows: (1) Whole-genome sequencing (WGS), with the first whole cancer genome to be sequenced being that of a cytogenetically normal myeloid leukemia.[29] Subsequently, several studies have employed this approach in the setting of breast cancer.[22,30,31] However, the implementation of WGS in clinical practice has been questioned, since the use of archived formalin-fixed paraffin-embedded tumor material is problematic. Additionally, high computational power and delicate bioinformatic tools are needed for data interpretation, posing further challenges in the clinical implementation of WGS.[32] (2) Targeted sequencing, referring to either whole-exome sequencing, or targeted-gene sequencing, is conducted using panels of selected cancer-related genes. Such approaches have certain advantages (Table 2), such as shorter turn-around times, lower costs, and less laborious data interpretation; presently, they are available in several Clinical Laboratory Improvement Amendments (CLIA)– certified laboratories; however, there is a compromise in the ability to detect translocations and other structural rearrangements.[33]

INNOVATIVE CLINICAL TRIAL DESIGNS

Currently, there is an increasing use of the afore-mentioned molecular profiling for patients with breast cancer, in particular in the setting of high-volume academic institutions, where extended profiling programs are being developed, sometimes in a CLIA environment.[34] Such initiatives can be used to guide patients in clinical trials assessing targeted agents.[35] However, several challenges can be identified, in regard to the success of trials assessing such experimental anticancer compounds (Table 3). To address these ever more frequently met challenges, new transformative clinical trial designs are needed. In such innovative trials, eligibility is based on the genotype of breast cancer, rather than the classic clinic-pathologic characteristic of the disease (Table 4). These study designs hold the promise to reduce the high attrition rates seen in oncology drug development, as well as to keep the number of patients recruited in the respective trials at reasonable levels. To this end, several innovative study designs are being developed.

TABLE 3. Challenges Encountered in Current Clinical Trials Assessing Targeted Anticancer Agents and Proposed Mechanisms to Circumvent Them

Phenomenon	Consequence	Potential Solution
Intertumor heterogeneity	Molecular fragmentation of the disease	· Innovative study designs such as master protocols to reduce screening failures · Statistical tools to reduce sample sizes needed (e.g., relaxing type I error) · Revisiting regulatory pathways for approval
	· Increased costs for molecular profiling	· Risk-sharing strategies · Greater pharmaceutical industry participation
	· Variable functional output of different aberrations	· Functional validation · Well-characterized xenograft tumor models
Intratumor heterogeneity	· Need to assess multiple molecular aberrations from one tumor sample	· Multiplexed molecular profiling to reduce tissue requirements · "Liquid" biopsies/plasma-based molecular profiling
	· Increased costs for molecular profiling	· Risk-sharing strategies · Greater pharmaceutical industry participation
Clonal evolution	· Emergence of treatment resistance	· "Liquid" biopsies/plasma-based molecular profiling
	· Discordances of aberrations between primary and metastatic disease	· Longitudinal cohorts of patients with profiling of both primary and metastatic tumor tissue · Biopsies/plasma-based molecular profiling

Longitudinal Cohort Studies with or without Downstream Clinical Trials

This study design can be exemplified by the AURORA (Aiming to Understand the Molecular Aberrations in Metastatic Breast Cancer) program initiated by the Breast International Group.[36] This represents a collaborative effort of European hospitals to conduct large-scale molecular profiling of patients with metastatic breast cancer who are prospectively followed (Fig. 1). This molecular profiling, of one metastatic lesion and of the primary tumor, can support the conduct of genotype-driven "nested" or "downstream" clinical trials,[37] offering a dual benefit: (1) facilitate the molecular preselection of patients eligible to be enrolled in genotype-driven clinical trials and (2) identify potential predictive biomarkers, through the coupling of the molecular and clinical outcome data captured for the patients enrolled in such a program. An important additional benefit that can be expected through this approach is the fact that clinicians become familiarized to the reporting of genomic data. Furthermore, such programs can improve our knowledge of prognosis for molecularly defined subsets of cancer, through the prospective follow-up of patients for clinical outcome. An already completed initiative from this category is the SAFIR01 program that recruited 423 patients with metastatic breast cancer.[38] Patients were subjected to biopsy of metastatic site, with the tissue analyzed by comparative genomic hybridization as well as Sanger sequencing of the *PIK3CA* and *AKT1* genes. This study, with a primary endpoint of the proportion of patients that could be entered into trials of targeted agents, demonstrated that personalization of treatment for patients with this disease is feasible in clinical practice. A subsequent effort, SAFIR02, is currently recruiting patients with HER2-negative metastatic breast cancer who have received no more than one line of chemotherapy. Metastatic tissue from these patients will be analyzed by NGS; after six to eight cycles of cytotoxic chemotherapy, patients with no progression of their disease will be randomly assigned to receive the standard of care or targeted therapy according to a list of 51 molecular alterations.

Studies Assessing the Clinical Utility of Molecular Profiling

The advent of molecular profiling in cancer has generated another study design, which assesses the clinical utility of

TABLE 4. Examples of Ongoing Genotype-Driven Clinical Trials in Breast Cancer

Clinicaltrials.gov Identifier	Phase (No. of Patients)	Genotype Targeted	Agent	Molecular Target	Design	Primary Endpoint
NCT01277757	II (40)	AKT mutations, PIK3CA mutations, PTEN loss	MK2206	AKT	Single-arm, monotherapy	ORR
NCT01219699	I (200)	PIK3CA mutations	BYL719	Alpha-isoform PI3K	Single-arm, BYL719 combined with fulvestrant	MTD
NCT01589861	I/II (106)	PIK3CA mutations, PTEN loss	BKM120	All isoforms PI3K	Single-arm, BKM120 combined with lapatinib	MTD, ORR
NCT01670877	II (29)	ERBB2 mutation	Neratinib	EGFR/HER2/HER4	Single-arm, monotherapy	CBR

Abbreviations: CBR, clinical benefit rate; EGFR, epidermal growth factor receptor; MTD, maximum tolerated dose; ORR, objective response rate; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PTEN, phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase.

FIGURE 1. The AURORA Initiative for Metastatic Breast Cancer

The AURORA Program

A prospective, longitudinal study of 1,300 women with Metastatic Breast Cancer recruited at 81 centers across 15 European countries
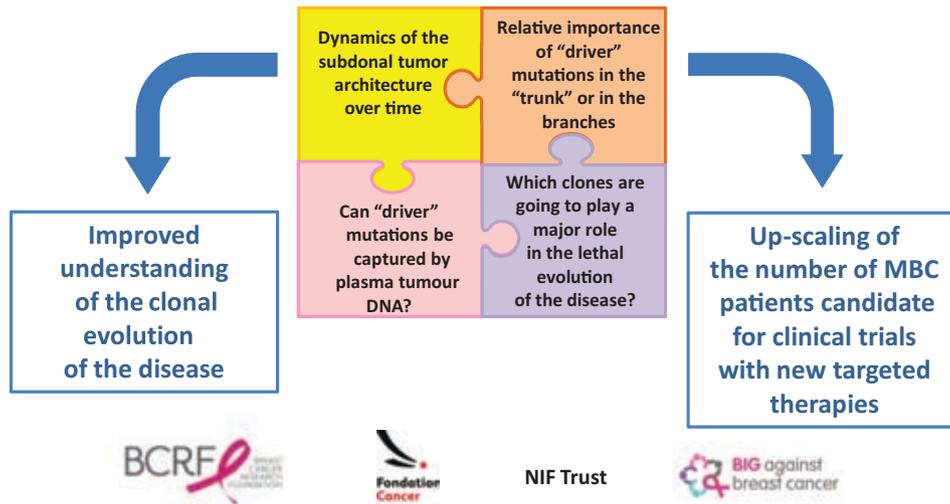
choosing targeted therapeutics based on the molecular profiling as compared with conventional treatment. This design does not assess individual targeted agents and should be therefore perceived as proof of concept. Tsimberidou et al reported promising results from a nonrandomized, phase I clinical trials program, according to which tumor tissue from patients with several advanced solid tumors diagnoses (1,144 tumors) were analyzed by molecular profiling: disease in patients having one molecular aberration who were treated based on the genotype of their disease (175 patients) demonstrated an increased overall response rate (27% vs. 5%; p < 0.0001), longer time-to-treatment failure (5.2 months vs. 2.2 months; p < 0.0001), and longer overall survival (13.4 vs. 9.0 months; p = 0.017) compared with patients who received conventional treatment (116 patients).[35] Currently, there is an ongoing randomized, proof-of-concept, phase II trial comparing targeted therapy based on tumor tissue molecular profiling compared with conventional treatment for patients with several advanced cancer types called SHIVA (NCT01771458).[39] This study incorporated a feasibility part, which demonstrated the feasibility and safety of incorporating biopsy of metastatic disease for the first 100 patients who enrolled.[40]

Master-Protocol Trials

This study design can assess different targeted agents in parallel within independent cohorts of patients defined by specific molecular aberrations that could predict sensitivity to the investigational agent under assessment. This approach reduces the percentage of screening failures, since patients with different aberrations can be enrolled in one of the different molecularly-defined cohorts. An important effort using this approach, recently initiated by the NCI, is the master protocol for second-line treatment of squamous NSCLC. An important effort using this approach recently initiated by the NCI is the master protocol for second-line treatment of squamous NSCLC. This trial will evaluate targeted agents matched to specific molecular segments of this type of cancer, with frequencies ranging between 9.3% and 20%. This is an initiative that aims to establish a novel approach to the clinical development of targeted agents and their subsequent regulatory approval, according to which treatment selection will be based on the results of NGS from a panel of approximately 250 cancer-related genes.[41] The study design that has been incorporated has five study strata with a total of 10 treatment arms; within each stratum a phase II/III study design has been adopted, with specific thresholds of efficacy that have to be met before moving to the phase III component. An important aspect of this trial that is currently recruiting patients is its collaborative nature, with multiple major partners working together, including the Southwestern Oncology Group, NCI, the Foundation for the National Institutes of Health, the Friends of Cancer Research, and the U.S. Food and Drug Administration. In the setting of breast cancer, the Breast International Group currently is designing such a study with input from the North American Breast Cancer Group, assessing targeted agents for patients with aggressive metastatic

triple-negative breast cancer. In particular, patients with this breast cancer phenotype whose disease develop early systematic relapse will be eligible. Once metastatic tumor tissue has been analyzed by NGS and upon availability of these results, the patients will be entered into one of multiple parallel, molecularly-driven arms, randomly assigned between the standard of care or the respective targeted agent(s), dictated by the genotype of their disease.

Basket Trials

This is an innovative, histology-independent trial design, in which patients with cancer diagnoses of different histologies can be enrolled in the study protocol based on the presence of a specific molecular aberration. There is an ongoing clinical trial that aims to develop a small molecule HER2 blocking agent for patients with *ERBB2*-mutated cancers that exemplifies this approach.[42] The main disadvantage in this innovative design is a biology-driven one; in particular this is the issue of the potentially different functional outputs that a specific molecular aberration could have among different types of cancer. This has been reported in studies documenting lack of antitumor efficacy of vemurafenib, a *BRAF* small molecule inhibitor, in the setting of *BRAF*-mutated metastatic colorectal cancer; these findings are in direct contradiction with the dramatic antitumor activity seen among patients with metastatic melanoma bearing the V600E *BRAF* mutation.[43] A major advantage of this study design is that it is very informative about which are the tumor types where single-agent therapy is worth pursuing in phase III trials versus other types where combination treatment strategies should be prioritized. Interestingly, there is an ongoing study by the NCI, called MATCH (Molecular Analysis for Therapy Choice) that combines elements from both master and basket trial design. In particular, this trial will assess molecularly targeted agents within specific molecular niches of cancer types such as erlotinib for EGFR-mutated NSCLC and crizotinib for cases with EML4-ALK translocations (master-trial component), as well as across different tumor types sharing a molecular aberration, e.g., vemurafenib in BRAF-mutated melanoma, thyroid cancer, and NSCLC (basket-trial component).

Adaptive Trials

Adaptive trials represent another transformative study design, recently exemplified by the BATTLE (Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination)-1 and -2 clinical trials, focusing on patients with metastatic NSCLC,[44] or the I-SPY (The Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Biomarker Analysis) 1 and 2 trials conducted in the neoadjuvant setting of breast cancer.[45-47] These are dynamically evolving trials, with the particular aspect of during the initial phase of the adaptive study patients are recruited in the different arms at an equal ratio; however, as more patients are enrolled and efficacy data are being generated and pooled from the different treatment arms, the adaptive phase follows. During this second, adaptive phase, randomization ratios can be changed and treatment arms can be dropped

and/or added, in cases where either predefined thresholds of efficacy are not reached or new promising data for new compounds emerge, respectively.[48] Additionally, in trials having an adaptive design, the biomarker selection strategy can be changed, even when the treatment assignment remains the same, depending on emerging evidence associating new biomarkers not previously identified with (lack of) sensitivity to one or more of the treatments under assessment.

N-of-1 Trials

This is a study design that has been more frequently employed in fields of clinical research other than oncology, such as trials conducted for patients with musculoskeletal or pulmonary conditions.[49,50] The defining characteristic is the recruitment of patients exposed to different experimental agents or placebo in different sequencing, with washout periods in between.[51] This type of design practically renders each involved patient to serve as his or her own comparator, through the comparison of the efficacy seen for the different experimental agents that the patient receives. In oncology, a modified N-of-1 study design has been performed, which assessed the antitumor activity of different anticancer compounds matched to the genotype of the patients.[52] This trial recruited 86 patients with different types of advanced tumor who had been heavily pretreated, that had molecular profiling. Sixty-six of these patients were treated according to these results. Concerning the efficacy, 18 patients had a PFS ratio of 1.3 or higher (95% CI, 17% to 38%; one-sided, one-sample $p = 0.007$). The study met its primary endpoint, which was the comparison of PFS obtained by the targeted treatment with the PFS achieved by the previous systemic treatment within each individual patient. This is an approach that could be of help for molecular aberrations of really low prevalence, where randomized studies are extremely challenging.

Window-of-Opportunity Trials

Window-of-opportunity trials incorporate a design assessing the administration of an investigational agent over a short period of time, most often in the presurgical setting allowing serial tumor biopsies, though such studies can be conducted in the metastatic setting as well.[53,54] These trials do not have an efficacy endpoint, since it is the in vivo biologic effects of an experimental agent and not the antitumor activity with officially predefined measures of outcome that they aim to assess. An ongoing study utilizing this innovative design is the D-beyond trial, a preoperative window study evaluating denosumab, a RANK ligand inhibitor, and its biologic effects for premenopausal women with early breast cancer.[55] Patients entering this trial receive preoperatively two doses of 120 mg of denosumab subcutaneously 1 week apart that will be followed by surgery. Ten to 21 days after the first administration, surgical excision of the primary tumor will take place; the primary objective is the antiproliferative effect exerted by denosumab, as indicated by Ki67 immunohistochemistry-based assessment. Another example of a window-of-opportunity trial that will soon be initiated is the RHEA (Biomarker Research Study for PF-03084014 in

Chemoresistant Triple-Negative Breast Cancer) trial. This is a single-arm, phase II, open-label, preoperative study of a small-molecule NOTCH inhibitor that is administered for 9 days after completion of neoadjuvant chemotherapy in patients with triple-negative breast cancer that is chemotherapy-resistant.

CONCLUSION

To the present day, great progress has been made in the molecular profiling of breast cancer, with an expanding array of molecular aberrations being identified. The subsequent development of experimental targeted agents promises to improve cancer treatment for patients bearing specific molecular aberrations. A major challenge is the assessment of the functional significance of such aberrations and the verification of their relevance as predictors of sensitivity to their matched targeted agents under development. The latter can be achieved through well-conducted clinical trials that match several specific genotypes of the disease with a number of targeted agents. To this end, innovative study designs must be implemented to expedite anticancer drug development. Such studies need to be coupled with next-generation molecular profiling techniques that have been validated to secure findings' reproducibility. The one-size-fits-all paradigm of conventional study design must be abandoned, and the approval strategies revisited in some cases. More extensive collaboration between academia around the world, regulatory agencies, and pharmaceutical companies developing new anticancer compounds is becoming a necessity for these innovative study designs to be successfully implemented.

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DEVELOPMENTAL THERAPEUTICS AND TRANSLATIONAL RESEARCH

The ABCs of Cancer Immunotherapy

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Managing Immune Checkpoint-Blocking Antibody Side Effects

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OVERVIEW

Immune checkpoint-blocking antibodies that enhance the immune system's ability to fight cancer are becoming important components of treatment for patients with a variety of malignancies. Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) was the first immune checkpoint to be clinically targeted, and ipilimumab, an inhibitor of CTLA-4, was approved by the U.S. Food and Drug Administration (FDA) for patients with advanced melanoma. The programmed cell death-1 (PD-1) receptor and one of its ligands, PD-L1, more recently have shown great promise as therapeutic targets in a variety of malignancies. Nivolumab and pembrolizumab recently have been FDA-approved for patients with melanoma and additional approvals within this therapeutic class are expected. The use of anti-CTLA-4 and anti-PD-1/PD-L1 antibodies is associated with side effects known as immune-related adverse events (irAEs). Immune-related adverse events affect the dermatologic, gastrointestinal, hepatic, endocrine, and other organ systems. Temporary immunosuppression with corticosteroids, tumor necrosis factor-alpha antagonists, mycophenolate mofetil, or other agents can be effective treatment. This article describes the side-effect profile of the checkpoint-blocking antibodies that target CTLA-4 and PD-1/PD-L1 and provides suggestions on how to manage specific irAEs.

The immune system plays an important role in controlling and eradicating cancer. Recently, strategies that enhance T-cell function by blocking negative regulatory components on T cells, which are called checkpoints, have led to remarkable success for patients with many different malignancies. CTLA-4 was the first T-cell checkpoint to be clinically targeted. Ipilimumab, an anti-CTLA-4 antibody, was approved by the FDA for patients with advanced melanoma based on an overall survival benefit.[1,2] A second immunologic checkpoint, known as PD-1, and its predominant ligand, PD-L1, also is demonstrating incredible promise as a therapeutic target. Nivolumab and pembrolizumab (anti-PD–1 blocking antibodies) have been FDA-approved for patients with advanced melanoma.[3,4] Nivolumab and pembrolizumab, and additional antibodies that target the PD-1 axis, are also effective in additional cancers such as non-small cell lung cancer, renal cell cancer, bladder cancer, and Hodgkin lymphoma.[5-9]

Although these antibodies can be associated with substantial benefits, by increasing immune system function, immune-checkpoint blockade can lead to inflammatory side effects called immune-related adverse events (irAEs). Immune-related adverse events can affect any organ system, but they typically involve the skin, gastrointestinal, hepatic, and endocrine systems. Temporary use of immunosuppressive medications can suppress these side effects without eliminating the possibility of a favorable antitumor response.

This review focuses on irAEs associated with antibodies that block the immunologic checkpoints, CTLA-4 and PD-1, including antibodies that block the ligand of PD-1/PD-L1. These agents have been studied most extensively in patients with melanoma, and experience and recommendations are based primarily on data obtained from studies involving patients with melanoma. Nevertheless, the principles of irAE recognition and management are relevant across the oncologic spectrum and will become increasingly important as the use of these antibodies expands.

SPECIFIC TYPES OF IMMUNE-RELATED ADVERSE EVENTS AND MANAGEMENT
Rash and Mucosal Irritation

The most common and typically earliest onset (Fig. 1) irAE associated with checkpoint inhibitors is dermatologic toxicity.[10] Nearly 50% of patients treated with ipilimumab will experience rash and/or pruritus. Rashes associated with checkpoint blockade often appear as faintly erythematous, reticular, and maculopapular. Typically, the trunk and extremities are involved.[11] In one case, neutrophilic infiltration, diagnostic of Sweet's Syndrome, was reported.[12] Vitiligo also can be seen, although it typically does not appear until months after the initiation of checkpoint blockade.

Topical corticosteroid creams can be used to treat rash induced by checkpoint blockade. Oral antipruritics (hy-

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FIGURE 1. Kinetics of Appearance of Immune-Related Adverse Events
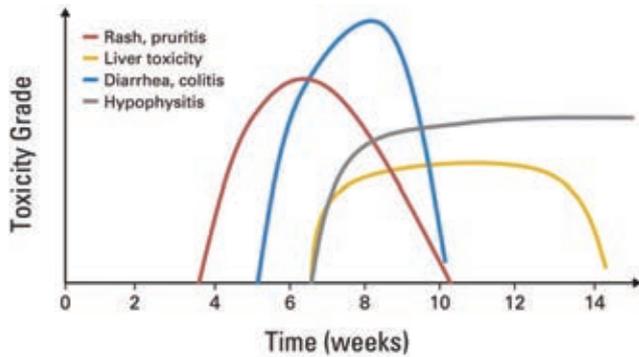
droxyzine HCl or diphenhydramine HCl) can help if pruritus is problematic. Severe rashes (grade 3 and above) should be managed with oral corticosteroids. Consideration of permanent discontinuation of checkpoint blockade because of reactions such as Stevens-Johnson syndrome/toxic epidermal necrolysis rarely have been reported. Such reactions require hospitalization for intravenous corticosteroids, dermatologic evaluation, and fluid/electrolyte management.

Antibodies that block PD-1/PD-L1 also can result in dermatologic/mucosal toxicity. Anecdotal cases of patients with oral mucositis and/or dry mouth symptoms have been described with PD-1/PD-L1 treatment. In a large phase I trial of nivolumab, 6.5% of patients had symptoms of dry mouth; one patient had symptoms of grade 3 dry mouth.[13] Oral corticosteroid rinses or lidocaine can treat this symptom effectively. Since many patients with this complaint may be receiving concomitant immunosuppression to treat another irAE, oral candidiasis remains in the differential diagnosis.

KEY POINTS

- Immune checkpoint-blocking antibodies can cause immune-mediated adverse events involving the skin, liver, gastrointestinal, endocrine, neurologic, and other organ systems.
- If appropriate immunosuppressive treatment is used, patients generally completely recover from immune-mediated adverse events.
- The use of immunosuppressive treatment to treat an immune-mediated adverse event does not impair the efficacy of immune-checkpoint blockade.
- There does not appear to be a strong correlation between the occurrence of an immune-mediated adverse event and long-term outcomes to immune checkpoint-blocking antibody therapy.
- Patients who stop immunotherapy because of side effects can still have excellent long-term outcomes.

DIARRHEA/COLITIS

Diarrhea is common in patients undergoing treatment with checkpoint-blocking antibodies. However, there is a much higher incidence of diarrhea in patients receiving CTLA-4 blocking antibodies compared to those targeting PD-1/PD-L1. When considering the occurrence of this irAE, distinguishing diarrhea (increase in frequency of stool) from colitis (abdominal pain, radiographic or endoscopic findings of colonic inflammation) is important. For patients with melanoma undergoing CTLA-4 blockade with ipilimumab, approximately 30% had diarrhea of any grade and less than 10% had severe (grade 3/4) diarrhea.[1] Rates of grade 3/4 colitis have been found to affect only approximately 5% of treated patients.[1,14] Patients should be informed that diarrhea/colitis does not typically begin with initiation of checkpoint blockade; instead, it usually begins approximately 6 weeks into treatment (Fig. 1).[15]

Diarrhea/colitis with CTLA-4 blockade is more common than with PD-1/PD-L1 blockade. The rate of grade 3/4 diarrhea in patients treated with PD-1/PD-L1 agents is very low (1% to 2%).[8,13,16] Although the precise safety profile is still under evaluation, patients who had significant diarrhea/colitis during CTLA-4 blockade have been treated with PD-1 therapy without diarrhea/colitis recurrence.[17] Nonetheless, ongoing trials and clinical experience are necessary to more fully understand the safety of PD-1/PD-L1 blockade in this setting.

When a patient presents with mild diarrhea, clinicians should consider other etiologies that may be responsible, such as *Clostridium difficile* infection or other bacterial/viral pathogens. Patients should be counseled on the importance of maintaining oral hydration. Some clinicians find that the American Dietary Association's colitis diet and antimotility agents (oral diphenoxylate HCl and atropine sulfate 4 times a day) can be helpful. If symptoms persist for more than 3 days, or increase, and/or no infectious causes are readily identified, the use of oral or intravenous corticosteroids are required.

In severe cases or situations in which symptoms do not improve with oral corticosteroids, hospitalization for intravenous corticosteroids, hydration, and electrolyte management is required. A colonoscopy is not necessarily indicated unless the diagnosis is unclear. If intravenous corticosteroids (up to 2 mg/kg methylprednisolone twice a day) do not lead to symptom resolution, infliximab (Remicade; Janssen Biotech, Horsham, PA) at a dose of 5 mg/kg, once every 2 weeks can be helpful.[18-20] The use of infliximab in this setting is based on its use in patients with inflammatory bowel diseases.[21] In very rare cases, colitis can result in bowel perforation that can potentially require colostomy.

Unfortunately, there are no proven treatments to prevent the occurrence of diarrhea. In one study, prophylactic use of the matrix-release corticosteroid budesonide was not found to be helpful.[22] Nevertheless, some clinicians find budesonide to be helpful in early treatment for mild noninfectious

diarrhea symptoms that persist but do not escalate after 2 to 3 days of dietary modification and antimotility agents.

HEPATOTOXICITY

Hepatitis, as determined by elevations in aspartate aminotransferase (AST), aminotransferase (ALT) and less commonly, total bilirubin, occasionally is seen in patients treated with checkpoint blockade. Although most episodes present only as asymptomatic laboratory abnormalities, some patients have an associated fever. Rates of AST and ALT elevations with CTLA-4 blockade vary among clinical trials, but they typically have been reported in less than 10% of patients.[14,23,24] In large trials of PD-1– blocking antibodies, the rates of hepatitis were similarly low (below 5%) and grade 3/4 toxicity was even rarer.[3,13,16]

Among patients who develop hepatitis, the most common onset is 8 to 12 weeks after initiation of treatment, although early or delayed events also may be seen (Fig. 1).[10] Radiographic findings are not typical. In severe cases, however, findings on CT scans may include mild hepatomegaly, periportal edema, or periportal lymphadenopathy.[25] Liver biopsies have described pathologic changes that include severe panlobular hepatitis with prominent perivenular infiltrate with endothelialitis or a primary biliary pattern with mild portal mononuclear infiltrate around bile ductules.[25,26]

Hepatic function (transaminases and bilirubin) should be monitored before each dose of ipilimumab. If AST and ALT increase, viral and other drug-induced causes of hepatitis should be excluded. As with treating other irAEs, if no other cause is obvious, prompt treatment with corticosteroids is necessary. In rare cases, elevations in AST and ALT are steroid-refractory and 500 mg every 12 hours of mycophenolate mofetil (CellCept; Genentech, South San Francisco, CA) may be helpful. The use of antithymocyte globulin therapy also was described in a case report.[27] Unlike for patients with diarrhea/colitis, infliximab should not be given to patients with hepatitis because infliximab carries a risk of hepatotoxicity. Hepatitis may persist for quite some time and require prolonged or repeated corticosteroid tapers (minimum of 3 weeks suggested) and/or additional immunosuppression.

ENDOCRINOPATHY

Immune-related adverse events that affect the pituitary, adrenal, and thyroid glands often present with nonspecific symptoms such as nausea, headache, and fatigue. The incidence of endocrinopathy has been difficult to precisely determine because of the variable methods of assessment, diagnosis, and monitoring in each clinical trial. Nonetheless, hypophysitis (pituitary inflammation) and hypothyroidism are the most common endocrinopathies and are typically believed to occur in up to 10% of patients treated with CTLA-4 blockade.[28,29]

When hypophysitis is suspected, all or some of the hormones released by the pituitary may be reduced (adrenocorticotropic hormone [ACTH], thyroid stimulating hormone [TSH], follicle stimulating hormone, luteinizing hormone, growth hormone, prolactin). Typically, hypophysitis is diagnosed by clinical symptoms of fatigue and headache, radiographic findings (enhancement and enlargement of the pituitary[30,31]), and biochemic evidence of pituitary dysfunction (low ACTH and TSH). Biochemical tests associated with hypophysitis are distinct from primary adrenal insufficiency (low cortisol or inappropriate cortisol stimulation test; high ACTH) and primary hypothyroidism (low free T4; high TSH).

When hypophysitis is suspected, some clinicians have anecdotally described that a course of high-dose corticosteroids (1 mg/kg of prednisone daily) given during the acute phase can reverse the inflammatory process and prevent the need for longer-term hormone replacement. In almost all patients, however, longer-term supplementation of affected hormones is necessary because of secondary hypothyroidism (treated with levothyroxine) or secondary hypoadrenalism (treated with replacement doses of hydrocortisone, typically 20 mg each morning and 10 mg each evening). Some authors have described that patients can be successfully weaned from replacement corticosteroids over time, but this is likely the exception.[32] The immunologic mechanisms of hypophysitis are unknown, but they may be related to the development of humoral (antibody) immunity against the pituitary gland and subsequent complement activation.[33]

Since routine monitoring of thyroid function tests (TSH) is required before each dose of ipilimumab, patients often are diagnosed with thyroid abnormalities (hyperthyroidism and hypothyroidism) as a result of checkpoint blockade. Hypothyroidism is believed to occur far more commonly than hyperthyroidism. When patients are evaluated for fatigue that is possibly a result of endocrinopathy, it is important to distinguish primary hypothyroidism (low free T4 and high TSH) from hypophysitis, which can result in secondary hypothyroidism (low free T4 and low TSH). Management of hypothyroidism involves replacement with thyroid hormone (levothyroxine).

The most emergent endocrinopathy is an adrenal crisis associated with dehydration, hypotension, and electrolyte imbalances such as hyperkalemia and hyponatremia. When this occurs, intravenous corticosteroids and immediate hospitalization is required. Consultation with an endocrinologist, aggressive hydration, and evaluation for sepsis is critical.

The frequency of endocrinopathy in patients treated with PD-1/PD-L1 agents is not known yet, but it may differ from those seen with CTLA-4 blockade. Hypophysitis rarely has been described in published trials of PD-1 blockade for patients with advanced melanoma.[3,13] Thyroid disorders have been described in less than10% of patients.[3,16] Some cases, however, can be severe.[34] Treatment of endocrinopathy with PD-1/PD-L1 agents is approached in a way similar to treating patients undergoing CTLA-4 blockade.

LESS FREQUENTLY INVOLVED ORGANS

Lung

Several pulmonary inflammatory conditions have been seen in patients treated with ipilimumab, including sarcoidosis[35,36] and organizing inflammatory pneumonia.[37] Pneumonitis also has been described in patients treated with PD-1 blocking agents (< 10%)[3,5,16,38] but with occasional fatal consequence in early trials.[5] In any patient presenting with pulmonary symptoms, such as an upper respiratory infection, new cough, or shortness of breath, pneumonitis should be considered and evaluated with imaging. In moderate to severe cases, a bronchoscopy should be performed to exclude infectious etiologies before starting immunosuppression. In severe cases, treatment should consist of high doses of corticosteroids such as 2 mg/kg of intravenous methylprednisone. Additional immunosuppression with infliximab, mycophenolate mofetil, or cyclophosphamide is reasonable.

Eye

Inflammation of components of the eye has been described with CTLA-4 blockade. These include episcleritis, conjunctivitis, and uveitis. Typically, the incidence is believed to be less than1%, and symptoms can include photophobia, pain, dryness of the eyes, and blurry vision.[39] Consultation with an ophthalmologist is recommended, and treatment with topical intraocular corticosteroids such as 1% prednisolone acetate suspension may be helpful. Oral corticosteroids can be used for more severe (grade 3/4 or refractory) cases. The incidence of ophthalmologic toxicity in patients treated with PD-1/PD-L1 blockade is less-well described, but it is likely an infrequent side effect.

Kidney

Several case reports have described patients treated with ipilimumab who have developed renal insufficiency believed to be related to treatment. Histopathologic analyses of kidney biopsies have described several different pathologic processes, including acute granulomatous interstitial nephritis[40] and lupus membranous nephropathy.[41] Treatment with oral or intravenous corticosteroids in these cases has been associated with improvement in renal function.[42,43] Renal insufficiency with PD-1 agents and the combination of CTLA-4 and PD-1 blockade similarly has been reported in several patients with anecdotal findings of interstitial nephritis and response to corticosteroids.[16,44]

Pancreas

The routine monitoring of amylase and lipase values in otherwise asymptomatic patients treated with checkpoint blockade is not recommended. Similarly, corticosteroids are not indicated in patients with asymptomatic elevations in amylase/lipase without other symptoms of pancreatitis. Nevertheless, when pancreatitis is suspected clinically, amylase and lipase should be checked since immune-related pancreatitis has been reported in patients treated with CTLA-4 and PD-1 blockade.[38,45] The high rate of asymptomatic elevations in amylase/lipase in clinical trials of patients receiving CTLA-4 and PD-1/PD-L1 blockade is of uncertain clinical significance since these patients did not meet the diagnostic criteria for pancreatitis.[46]

Neurologic Syndromes

Neurologic syndromes have been associated with checkpoint blockade with ipilimumab. These include posterior reversible encephalopathy syndrome,[47] aseptic meningitis,[48] enteric neuropathy,[49] and transverse myelitis.[50] Cases of Guillain-Barre syndrome are particularly notable[51] because one case resulted in a treatment-related death in a postsurgical adjuvant study of ipilimumab.[52] As with other irAEs, corticosteroids can be helpful. In consultation with a neurologist, plasmapheresis and intravenous immunoglobulin may be considered.

Hematologic Syndromes

Red cell aplasia,[53] neutropenia,[54] and acquired hemophilia A[55] also have been described in patients treated with ipilimumab, as has thrombocytopenia.[56] Similar to many of the irAEs described above, the standard approach remains initial immunosuppression with corticosteroids. A bone marrow biopsy may be necessary in some cases, particularly when the diagnosis remains unclear.

IMMUNE-RELATED ADVERSE EVENTS ASSOCIATED WITH COMBINATION OF CONCURRENT CTLA-4 AND PD-1 BLOCKADE

The distinct action mechanisms of CTLA-4 and PD-1 blockade have led to investigations treating patients with both CTLA-4 and PD-1/PD-L1 in those who develop a variety of malignancies. Published data on the combination of ipilimumab and nivolumab exist for patients with advanced melanoma.[44] The rate of published grade 3/4 treatment-related adverse events related to therapy in patients receiving this treatment is approximately 50%, which is numerically higher than rates described for patients receiving either CTLA-4 or PD-1/PD-L1 agents as single agents.[1,3,5,8,16] Many grade 3/4 irAEs in this trial, however, were asymptomatic, abnormal laboratory values. This included a high rate of patients with asymptomatic elevations in lipase (over 10%), none of whom developed pancreatitis. No new toxicities were attributed to the combination of ipilimumab and nivolumab that have not been seen with ipilimumab or nivolumab alone.

The combination of ipilimumab and nivolumab may have a different safety profile in patients with other advanced malignancies, and this combination remains under active investigation. Other studies seek to test similar combinations using different CTLA-4 and PD-1/PD-L1– blocking antibodies (NCT01975831, NCT02089685, NCT01928394).

COMBINATION OF IMMUNE CHECKPOINT-BLOCKING ANTIBODIES AND TARGETED THERAPY

The treatment of many malignancies has improved with the discovery of oncogenic proteins amenable to targeted inhibi-

tion. One of these momentous advances has been targeting mutant *BRAF* and the mitogen-activated protein (MAP) kinase pathway in patients with melanoma.[57-62] Based on preclinical evidence that suggests RAF inhibitors can have positive immunologic effects,[63-68] there has been great interest in exploring combinations of targeted agents that inhibit mutant *BRAF* with immune checkpoint- blocking antibodies.

The toxicity profile of combinations of targeted agents and immune-checkpoint blockade, however, is just beginning to be explored. In the only published prospective study, treatment with vemurafenib and ipilimumab was associated with a high rate of grade 3 transaminase elevations that required cessation of further exploration of this combination as concurrent therapy.[69] Rash was also an important problem with this combination, which is consistent with similar findings when vemurafenib was administered soon after completing ipilimumab.[70]

The irAE profile of ipilimumab in combination with RAF inhibitors may vary by specific RAF inhibitor. In a separate phase I study, dabrafenib was combined with ipilimumab and preliminarily, no major safety concerns with this doublet combination have been seen.[71] The safety of ipilimumab with dabrafenib and trametinib, however, may be more problematic because some patients treated with this triplet had severe colitis with perforation.

Future investigations of targeted agents and immune checkpoint-blocking antibodies should continue in patients who develop multiple diseases, and that dose and schedule will be critical to the safety and possibly efficacy of these combination approaches. It is expected that combinations of targeted agents with PD-1/PD-L1 antibodies may show a more favorable side-effect profile than combinations with ipilimumab; however, this is the subject of ongoing investigation.

COMBINATION OF IPILIMUMAB AND GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR

Granuloycte-Macrophage Colony-Stimulating Factor (GM-CSF) (Leukine; Genzyme, Ridgefield, NJ) currently is not indicated to prevent or treat irAEs. Nonetheless, combining GM-CSF with immune-checkpoint blockade is of interest based on favorable preclinical data suggesting GM-CSF–secreting tumor vaccines enhanced the activity of CTLA-4 blockade.[72] The combination of GM-CSF and ipilimumab was tested in patients with advanced melanoma in a phase II randomized study (ipilimumab 10 mg/kg plus GM-CSF vs. ipilimumab 10 mg/kg alone). Interim results indicate that the combination prolonged survival and was associated with fewer irAEs than ipilimumab 10 mg/kg alone.[73]

Reasons for the decreased rate of side effects are unclear, but GM-CSF has been implicated in the pathogenesis of inflammatory bowel disease.[74] Whether GM-CSF would result in similar effects in patients treated with the commercially available dose of ipilimumab (3 mg/kg) is unknown. Additional studies are necessary before GM-CSF is routinely recommended for patients being treated with ipilimumab.

OPPORTUNISTIC INFECTIONS IN IMMUNOSUPPRESSED PATIENTS

Since prolonged immune suppression is occasionally used to treat irAEs, patients can be at risk for unusual or opportunistic infections. Though anecdotal cases of these infections, such as *Aspergillus* pneumonia, have been reported,[75] the true incidence of these opportunistic infections remains unknown. *Pneumocystis jiroveci* prophylaxis with cotrimoxazole, atovaquone, or pentamidine should be considered in patients treated with 20 mg of prednisone equivalent daily for at least 4 weeks, based on the National Comprehensive Cancer Network guidelines for the Prevention and Treatment of Cancer-Related Infections (Category 2B recommendation). The role of prophylactic antiviral or antifungal therapy in this setting is unclear.

INVESTIGATIONS CORRELATING IMMUNE-RELATED ADVERSE EVENTS WITH EFFICACY

The correlation between efficacy of checkpoint-blocking antibodies and the occurrence of irAEs is controversial.[76,77] Patients can benefit from checkpoint-blocking antibodies without developing irAEs. Any potential association between PD-1/PD-L1– blockade and irAEs will be hard to determine as the incidence of significant irAEs is low.

SAFETY OF IMMUNE-CHECKPOINT INHIBITION IN PATIENTS WITH UNDERLYING AUTOIMMUNE CONDITIONS

The safety of immune-checkpoint inhibitors in patients with an unrelated autoimmunity disorder (e.g., rheumatoid arthritis, systemic lupus erythematosus) is unknown. Both CTLA-4 and PD-1 have an important function in maintaining immunologic homeostasis, and there is theoretic concern that therapeutic blockade of these receptors could lead to exacerbations of underlying autoimmune conditions. Preclinical models suggest CTLA-4 blockade can exacerbate autoimmune diseases.[78,79] Since patients with underlying autoimmune conditions were not included in clinical trials of checkpoint-blocking antibodies, clinical evidence of the safety of this approach requires further study. Anecdotally, some patients with underlying autoimmune conditions have been treated safely with ipilimumab,[80,81] but one patient with multiple sclerosis reported worsening symptoms after ipilimumab.[82] Given the profound potential benefits of these checkpoint- blocking antibodies in patients with life-threatening malignancies, clinicians should engage patients with autoimmune diseases in thoughtful discussion about the possible benefits and risks of immunologic checkpoint blockade.

CONCLUSION

Immunologic-checkpoint inhibition targeting CTLA-4 and PD-1/PD-L1 has dramatically improved the care of patients

with many advanced malignancies. Treatment is associated with typically transient irAEs, but irAEs occasionally can be severe and fatal. Rapid identification of these side effects and initiation of systemic immunosuppression can improve outcomes without compromising the efficacy of immune-checkpoint inhibition. Although no prospective data exist to guide recommendations for the best specific immunosup-

pressive treatment, adherence to established guidelines based upon collective clinical experience is recommended. Clinical experience with immune-checkpoint inhibitors in a variety of disease settings and in novel combinations ultimately will refine knowledge and management of irAEs and provide the opportunity to obtain the full therapeutic potential of this promising treatment modality.

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GASTROINTESTINAL (COLORECTAL) CANCER

Locally Advanced Rectal Cancer: Time for Change?

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Locally Advanced Rectal Cancer: Time for Precision Therapeutics

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OVERVIEW

The year 2015 marks the 30th anniversary of the publication of NSABP-R01, a landmark trial demonstrating the benefit of adding pelvic radiation to the treatment regimen for locally advanced rectal cancer with a resultant decrease in local recurrence from 25% to 16%. These results ushered in the era of multimodal therapy for rectal cancer, heralding modern treatment and changing the standard of care in the United States. We have seen many advances over the past 3 decades, including optimization of the administration and timing of radiation, widespread adoption of total mesorectal excision (TME), and the implementation of more effective systemic chemotherapy. The current standard is neoadjuvant chemoradiation with 5-fluorouracil (5-FU) and a radiosensitizer, TME, and adjuvant chemotherapy including 5-FU and oxaliplatin. The results of this regimen have been impressive, with a reported local recurrence rate of less than 10%. However, the rates of distant relapse remain 30% to 40%, indicating room for improvement. In addition, trimodality therapy is arduous and many patients are unable to complete the full course of treatment. In this article we discuss the current standard of care and alternative strategies that have evolved in an attempt to individualize therapy according to risk of recurrence.

The current standard of care for patients with stage II (T3/T4N0) and stage III rectal cancer (TanyN1/N2) is trimodality therapy including chemotherapy, radiation, and surgery with complete TME.[1] The primary rationale for systemic chemotherapy is to reduce the risk of distant recurrence, whereas the rationale for pelvic radiation is to prevent local recurrence and, in some cases, convert a patient from requiring abdominoperineal resection—which requires a permanent ostomy—to a sphincter-sparing low anterior resection. The trimodality approach has gained widespread acceptance, with numerous publications reporting a substantial reduction in local recurrence rates and prolongation of disease-free survival.[2-6] Since its inception, progress within each of the three therapeutic modalities has continued.

The decision to use short-course radiotherapy (25 Gy in 5 fractions) versus long-course therapy (50.4 Gy delivered in 28 fractions with concurrent fluoropyrimidine) has largely depended on geography. Short-course regimens are generally favored in Northern Europe and Scandinavia, whereas long-course chemoradiation is advocated in North America and Central Europe. A Polish randomized trial compared long-course and short-course radiochemotherapy in patients with T3/4 mid- to low-lying rectal tumors, investigating the efficacy of each regimen. Higher rates of complete pathologic response were observed in patients treated with long-course chemoradiotherapy (16% vs. 1%). Although the rate of positive circumferential resection margin (CRM) was signifi-

cantly higher in patients receiving short-course therapy (13% vs. 4%; p = 0.017), no differences in local recurrence, disease-free survival, or overall survival were observed.

The German CAO/ARO/AIO 94 trial, published 11 years ago, compared preoperative and postoperative long-course chemoradiotherapy for stage II and III rectal cancer.[7] The preoperative treatment group demonstrated a significant (p = 0.006) decrease in local recurrence rate after 5 years, without a difference in rates of distant metastasis or overall survival. Additional benefits of preoperative versus postoperative chemoradiation included a significant decrease in short-term and long-term toxicity; for example, the incidence of grade 3 or higher toxicity was reduced from 40% in the postoperative group to 27% in the preoperative group (p = 0.001). Over the past decade, preoperative chemoradiation has become the standard of care in the United States. Although this shift has certainly reduced treatment toxicity for many patients, many clinicians have questioned whether it has also resulted in excessive radiation exposure for individuals with easily resectable tumors (e.g., T3N0) who might not have required any pelvic radiation at all had they first undergone surgery.

TME involves removal of the rectum together with its cylindrical mesentery and associated nodal tissue. The development and dissemination of this technique represented an incremental advance in oncologic surgery. TME involves sharp dissection between the visceral and parietal layers of

the endopelvic fascia. Anatomic resection ensures complete removal of all locoregional lymph nodes, while maintaining negative CRMs, minimizing blood loss, and preserving the autonomic pelvic nerves. Although no prospective randomized trial has compared TME with conventional proctectomy, numerous retrospective and cohort studies demonstrate excellent local recurrence-free survival in patients undergoing TME.[8-10]

The Dutch trial, published in 2001, was the first study to integrate TME into a control arm and underscored the importance of quality surgical technique. This trial compared the combination of preoperative radiation therapy and TME to TME alone, demonstrating a significant (p < 0.001) decrease in local recurrence in patients receiving preoperative short-course radiation. Critics have argued that, although the quality of surgery was controlled, up to one-quarter of patients had inadequate mesorectal excision on pathologic analysis, which led to a significantly worse outcome (p = 0.02).[11] Long-term follow-up demonstrated that certain patient sub-groups—those with node involvement, negative CRMS, and/or low-lying tumors (within 5–10 cm of the anal verge)—obtained the greatest benefit from preoperative radiation.[12,13] These findings suggested that some sub-groups treated with multimodality therapy may benefit less from the addition of chemoradiation. Furthermore, neoadjuvant radiation did not improve overall survival.

Current data support the use of either single-agent 5-FU or oral capecitabine with concurrent radiation therapy. A recent large randomized study comparing infusional 5-FU to oral capecitabine showed equivalent efficacy.[14] This trial also demonstrated that concurrent use of oxaliplatin with radiation adds to toxicity but does not improve efficacy; therefore, this approach is not recommended.[14,15] Extrapolating from data on colon cancer, postoperative oxaliplatin-containing regimens such as FOLFOX are typically used in the setting of rectal cancer. Adjuvant chemotherapy begins 4 to 6 weeks after surgery and administration of 12 cycles is standard, although discontinuing oxaliplatin upon early signs of neuropathy is essential to prevent long-term impairment.

Although use of chemoradiation as initial management is now standard practice, there has been growing interest in the use of systemic oxaliplatin-containing chemotherapy first,

followed by chemoradiation, for locally advanced disease. Chau et al published data on an initial series of patients with locally advanced, poor-risk rectal cancer who were treated with CapeOx for 3 months, followed by capecitabine plus radiation therapy.[16] The radiologic response rate was 88%, and 86% of patients achieved symptomatic response at a median of 32 days. A recent single-center retrospective study on the use of initial induction FOLFOX chemotherapy in patients with locally advanced rectal cancer demonstrated high response rates. Notably, this treatment strategy enabled the delivery of virtually all planned systemic chemotherapy without limiting the ability to deliver the planned chemoradiotherapy.[17] Patients were routinely re-evaluated by their surgeons after approximately 8 weeks of chemotherapy to rule out local progression, and no patient in this series was reported to have local progression at the time of examination. All patients undergoing TME surgery achieved an R0 resection.

This concept of "chemotherapy first" with 4 months of FOLFOX or CapeOx, followed immediately by chemoradiotherapy and then TME, is a logical extrapolation from current practice. It is clear that there never will be an adequately powered, randomized phase III trial of "chemo first" versus the current routine of "chemo last"; however, there are several reasons for delivering all planned therapy before resection with the expectation that this would be advantageous. Advantages include introduction of the best systemic therapy as early as possible, thus maximally addressing concerns over distant micrometastatic disease and enabling the rapid initiation of chemotherapy to obtain symptomatic relief. Patients who are treated with chemotherapy as a first-line approach have a high likelihood of receiving all planned chemotherapy, which is less often the case when chemotherapy is planned postoperatively. Furthermore, diverting ostomies can be closed substantially earlier when no postoperative chemotherapy is required. This approach is especially attractive in the setting of bulky tumors and radiographic evidence of tumor involvement of the radial circumferential mesorectal margin, adjacent organs (prostate or vagina), or numerous locoregional lymph nodes.

Although the oncologic results of combined modality therapy for rectal cancer are impressive, trimodality treatment is difficult to endure. This has led many clinicians to question whether treatment can be simplified. Investigators have approached this by trying to tailor therapy and selectively omit one of the three major treatment modalities. For example, one suggested approach is elimination of systemic chemotherapy for patients who have favorable pathologic stage after neoadjuvant treatment. Another approach pioneered by Brazilian investigators is to selectively omit surgical resection for individuals with clinical complete response to neoadjuvant chemoradiation. Finally, in North America, there has been interest in using pelvic radiation selectively for those patients at greatest risk of pelvic recurrence.

The rationale for selective use of pelvic radiation stems from its short- and long-term morbidities. Neoadjuvant chemoradiation is taxing and time intensive, requiring daily treatment for 5 weeks, and compliance is frequently poor.[18]

KEY POINTS

- Combined modality therapy—including chemotherapy, radiation, and surgery—is the standard for locally advanced rectal cancer.
- Pelvic radiation reduces local recurrence but does not reduce distant relapse or improve overall survival.
- A noteworthy portion of patients are unable to complete the prescribed treatment for rectal cancer.
- Total neoadjuvant therapy attempts to deliver all therapy prior to surgery.
- PROSPECT is an international randomized trial attempting to individualize rectal cancer treatment.

Debilitating short-term toxicities have been reported in up to 50% of patients,[19] with up to 70% unable to complete the entire course of treatment.[18] Additionally, the long-term effects of radiation can lead to disabling complications. Radiation-related fibrosis and autonomic nerve injury are associated with increased fecal incontinence, urgency, and frequency, and higher rates of sexual and genitourinary dysfunction have also been observed. Overall quality of life is poor compared with that of patients who do not receive chemoradiation.[7,18,20-22] Finally, chemoradiation may impair bone marrow reserve, which complicates the ability to deliver systemic chemotherapy in the metastatic setting.

The current paradigm treats all patients with stage II and III rectal cancer alike. However, many experts question whether all of these patients should be treated as a homogeneous group. There is growing evidence that not all patients with stage II and III disease are high risk, and a more individualized approach has been advocated. The rationale for change is based on (1) treatment-related toxicities, (2) concerns regarding a delay in systemic chemotherapy, and (3) the potential for unnecessary overtreatment.

Gunderson et al demonstrated that the risk of local recurrence in patients with rectal cancer can be stratified by T and N stage using an aggregation of data from several phase III North American rectal cancer adjuvant trials (NCCTG 794751, NCCTG 864751, and U.S. GI Intergroup 0114).[23] TN stage was categorized according to risk of recurrence: low (T1/2N0), intermediate (T1/2N1, T3N0), moderately high (T1/2N2, T3N1, T4N0), and high (T3N2, T4N1/2). Patients with intermediate-risk tumors had better outcomes than patients with moderately high and high-risk tumors, including lower rates of local recurrence (6 to 8% vs. 8 to 15% and 15 to 22%, respectively) and improved overall survival (74 to 81% vs. 61 to 69% and 33 to 48%).[23] These data suggest that routine adjuvant radiation therapy may not be required for intermediate-risk tumors (T1/2N1 or T3N0) when TME with negative radial margins has been performed.

The final analysis of the Intergroup 0114 trial reported similar findings[24]; however, these are based on limited data and the conclusions are difficult to substantiate because all patients received radiation therapy. A second pooled analysis attempted to dissect the effect of treatment on outcome.[25] Data from five phase III North American rectal cancer trials conducted over a 13-year period (NSABP R01, NSABP R02, NCCTG 794751, NCCTG 864751, and U.S. GI Intergroup 0114) were aggregated, and the subsequent analysis of 3,791 patients compared outcomes according to TN stage and various treatment regimens: surgery alone (179 patients), surgery and radiation (281 patients), surgery and chemoradiotherapy (2,799 patients), or surgery and chemotherapy (532 patients). In the setting of intermediate-risk tumors (T1/2N1 and T3N0), no additional benefit in disease-free survival or overall survival was observed when adding radiation to chemotherapy after surgery. These analyses demonstrate heterogeneity in the risk of local recurrence, and provide a rationale for individualizing treatment.

A small pilot trial explored the use of initial therapy with FOLFOX-based chemotherapy, without planned radiation therapy, for locally advanced rectal cancer. The study cohort included 30% stage II and 70% stage III mid- to low rectal cancers. Of the 30 patients receiving chemotherapy alone, all had complete R0 resection and eight (27%) achieved a pathologic complete response with no viable tumor detected in the resection specimen.[26] All three patients who suffered recurrence had pulmonary metastasis, but no locally recurrent disease was observed. Nevertheless, delivery of preoperative chemotherapy without the routine use of radiation remains an experimental approach. It is currently being evaluated in the National Cancer Institute Cooperative Group PROSPECT trial, and at the present time should not be routinely used outside of a clinical trial.

PROSPECT (Fig. 1) is a large-scale, multi-institutional phase II/III randomized prospective trial comparing neoadjuvant FOLFOX with selective use of chemoradiation (NCCTG-N1048, NCT01515787). The study randomly and

FIGURE 1. Protocol Schema for NCCTG-N1048
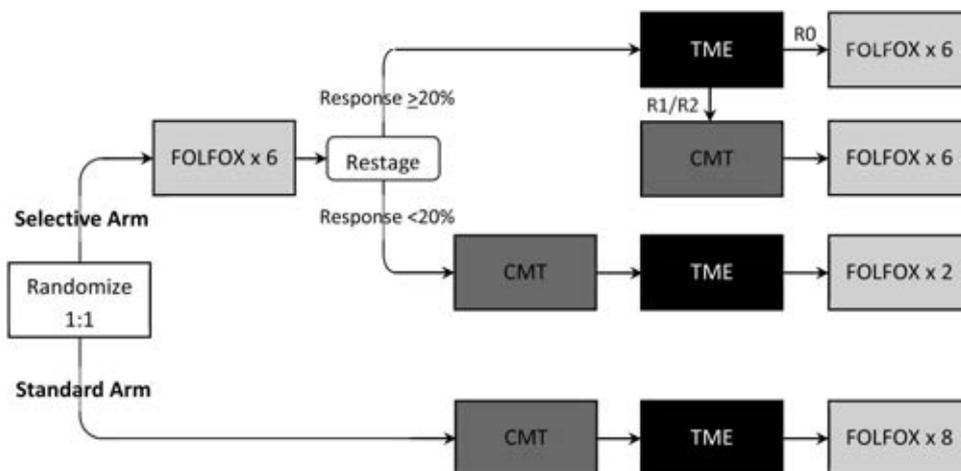
This ongoing phase II/III trial investigates whether standard combined modality treatment (CMT: 5-FU or capecitabine-based chemoradiation) can be replaced with selective use of neoadjuvant FOLFOX.

equally assigns patients with T1/2N1, T3N0, and T3N1 rectal cancer with tumors that are amenable to sphincter-preserving procedures, and without at-risk radial CRM, to either the "standard" or "selective" arm. Treatment in the standard arm consists of preoperative 5-FU or capecitabine-based chemoradiation, followed by TME and eight cycles of FOLFOX. Patients assigned to the selection arm receive six cycles of neoadjuvant FOLFOX and are then restaged. If clinical response to chemotherapy is observed in 20% or more of patients, the patients immediately proceed to surgical resection and adjuvant FOLFOX (6 cycles); however, if tumor response is less than 20%, the patients receive conventional combined-modality therapy before surgical resection and adjuvant FOLFOX (2 additional cycles). Patients in the selective arm who are found to have positive CRMs on final pathology undergo chemoradiation because of the increased risk for local recurrence. This study will determine whether neoadjuvant FOLFOX with selective use of chemoradiation can be safely used as an alternative to standard chemoradiation without compromising the ability to perform a margin-negative surgical resection, achieve local control, and improve overall disease-free survival.

In summary, there has been substantial progress in rectal cancer therapy in the past decade. Now, the field is ready for precision medicine, with tailoring of treatment to individual patient risk. Advances in chemotherapy, surgery, radiation, and imaging have each enabled tailoring of treatment. Although some patients still do not receive beneficial adjuvant and neoadjuvant treatments, at the same time the neoadjuvant paradigm means that others receive too much treatment. Current trials, including PROSPECT, are attempting to meet these challenges and develop individualized treatment based on personal risk, thus maximizing oncologic outcome and quality of life while limiting treatment-related toxicity.

Disclosures of Potential Conflicts of Interest

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GASTROINTESTINAL (COLORECTAL) CANCER

Sequence, Duration, and Cost of Treating Metastatic Unresectable Colorectal Cancer

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Biologic Therapies in Colorectal Cancer: Indications and Contraindications

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OVERVIEW

The role of antiangiogenic and anti-epidermal growth factor receptor (EGFR) agents has been investigated extensively in colorectal cancer in the palliative, adjuvant, and neoadjuvant settings. Although the role of biologic agents has become well-defined in the first, second, and subsequent lines of treatment of metastatic colorectal cancer (mCRC), considerable debate continues around the optimal sequencing and around optimal patient selection. The benefits from integrating bevacizumab or cetuximab in the adjuvant setting have been investigated in several randomized phase III clinical trials in stage II/III disease, all with disappointing results. Neoadjuvant approaches incorporating biologic therapy in patients with liver metastatic disease have led to mixed results. Although the current evidence does suggest increased down-staging and increased resectability with the addition of cetuximab in patients with initially unresectable or borderline resectable liver metastases, a positive effect of anti-EGFR therapy on the overall survival (OS) in this setting is not conclusive. Patients with resectable liver metastases derive no benefit and may experience potential harm from the addition of cetuximab to neoadjuvant chemotherapy. Similarly, there is neither rationale nor adequate data to support the addition of bevacizumab to neoadjuvant chemotherapy in patients with resectable liver metastases. In this review, we examine the role of antiangiogenesis and anti-EGFR therapies across the spectrum of adjuvant, neoadjuvant, and metastatic disease.

Significant progress has been made in the last decade in the management of mCRC, with median OS of patients with mCRC now at or exceeding 30 months.[1,2] The improvements in outcome are at least partially credited to the integration of biologic therapies, whether antiangiogenic or anti-EGFR, in the mainstream treatment of metastatic disease. Although significant progress has been made with the addition of these classes in advanced noncurable disease, their role has been disappointing in the adjuvant setting and continues to evolve in the neoadjuvant setting. In this review, we will summarize the current clinical data for biologic and targeted agents in adjuvant CRC, neoadjuvant, and nonresectable mCRC.

BIOLOGIC THERAPY IN THE ADJUVANT TREATMENT OF COLORECTAL CANCER

Bevacizumab in Stage II and III Colon Cancer

Several randomized phase III clinical trials have evaluated bevacizumab in combination with systemic chemotherapy in the adjuvant treatment of colorectal cancer. The NSABP C-08 clinical trial randomized 2,710 patients with stage II or III colon cancer to receive 6 months (12 cycles) of modified FOLFOX6 regimen with or without 1 year of bevacizumab.[3,4] No significant effect on disease-free survival (DFS) or OS was noted in the study population or within the stage II or stage III subgroups. Interestingly, the effect of bevacizumab on DFS was different before and after the 15-month time point from study treatment. The hazard ratio (HR) for recurrence within 15 months from start of study treatment was 0.61 (95% CI, 0.48 to 0.78) in favor of bevacizumab. In contrast, a trend toward increased recurrence rate was noted after 15 months on the bevacizumab arm. A post hoc analysis of the NSABP-CO8 population by mismatch repair status suggested a benefit from bevacizumab in the mismatch deficient cohort (HR 0.52; 95% CI, 0.29 to 0.94).[5] The AVANT phase III clinical trial randomized patients with stage II or III colon cancer to receive 6 months of oxaliplatin plus a fluoropyrimidine with or without bevacizumab.[6] Patients were randomly assigned in a 1:1:1 ratio to three arms of treatment: FOLFOX4, FOLFOX4 plus 1 year of bevacizumab, XELOX plus 1 year of bevacizumab. No benefits in DFS were noted with the addition of bevacizumab to chemotherapy. The HR for DFS for bevacizumab/FOLFOX4 and bevacizumab/XELOX compared with FOLFOX4 were 1.17 (95% CI, 0.98 to 1.39) and 1.07 (95% CI, 0.9 to 1.28), respectively. Similar to the NSABP-C08 study, bevacizumab was associated with an improved DFS in the initial period of follow-up. In the first year of the study, the HR for DFS was 0.63 and 0.61 on the bevacizumab/FOLFOX4 and bevacizumab/XELOX arms in comparison with FOLFOX4. This initial improvement in DFS

was offset by a detrimental effect of bevacizumab in DFS in years 2 and 3, leading to an overall trend to increased recurrences on the bevacizumab arms. This rebound increase in recurrences in the bevacizumab arms translated into a trend toward a detriment in OS in both the bevacizumab/FOLFOX4 and bevacizumab/XELOX arms when compared with FOLFOX4. Finally, the QUASAR2 study randomized 1,941 patients with stage III or high-risk stage II colorectal cancer to receive eight cycles of capecitabine (24 weeks) with or without 16 cycles of every 3-week bevacizumab (48 weeks).[7] An initial trend in improvement in DFS was noted in the bevacizumab arm in the first 2 years of follow-up. However, further follow-up after 2 years was associated with an increased recurrence rate in the bevacizumab arm, leading to a final HR for DFS of 1.06 in the bevacizumab arm compared with the control arm. Subgroup analysis in the microsatellite stable (MSS) and microsatellite instability (MSI) groups showed a significant detriment with bevacizumab in the MSS group (HR 1.43, $p = 0.0005$), whereas no significant difference in outcomes was noted in the MSI group (HR 0.74, $p = 0.42$).

No benefit is expected from the addition of bevacizumab to adjuvant cytotoxic chemotherapy in patients with stage II or III disease. To the contrary, worrisome trends toward increased recurrence rate after completion of bevacizumab therapy have been noted and have translated in a trend toward a worsened OS. The favorable trends noted with bevacizumab in tumors with MSI are hypothesis generating and may warrant further investigation in this subgroup of patients.

KEY POINTS

- There is no role for biologic therapy in the adjuvant treatment of colorectal cancer.
- In the setting of resectable metastatic disease to the liver, there is no evidence to suggest a benefit from adding either antiangiogenic or anti-epidermal growth factor receptor (EGFR) therapy. The addition of anti-EGFR therapy to chemotherapy in the neoadjuvant treatment of KRAS-wild type (WT) resectable liver metastases has been associated with a detrimental effect on disease-free survival.
- In patients with unresectable but potentially resectable disease, consideration for neoadjuvant FOLFOXIRI/bevacizumab (good performance status) or combination chemotherapy plus anti-EGFR agents (RAS-WT) should be made to increase the chances of curative-intent surgery.
- In RAS-mutant type or BRAF-MT metastatic colorectal cancer (mCRC), the continuum of angiogenesis targeting during the first two lines of treatment is recommended.
- Bevacizumab or anti-EGFR therapy in the first-line therapy of RAS-WT and BRAF-WT mCRC is acceptable with no clear evidence of superiority of one approach compared with another.

Cetuximab in the Adjuvant Treatment of Colorectal Cancer

The role of anti-EGFR therapy in the adjuvant treatment setting has been investigated through the N0147 and PETACC-8 clinical trials.[8,9] The initial design of the N0147 included a randomization to 6 months of FOLFOX, FOLFIRI, or sequential FOLFOX followed by FOLFIRI, with or without cetuximab in patients with stage III colon cancer. Subsequent protocol amendments resulted in the closure of the FOLFIRI and sequential FOLFOX/FOLFIRI arms, as well as the limitation of enrollment to patients with KRAS-wild type (WT) tumors.[8] The study accrued 2,070 patients with KRAS-WT tumors. No benefit in 3-year DFS in the cetuximab/FOLFOX compared with the FOLFOX arm was noted in the KRAS-WT (HR 1.21; 95% CI, 0.98 to 1.49) or KRAS/BRAF-WT populations. No advantage to the addition of cetuximab was noted in any of the subgroup analyses. Of note, no definitive conclusions could be deduced from the FOLFIRI cohorts on N0147 because of the small sample size. However, a trend toward improved DFS and OS was noted in the cetuximab/FOLFIRI compared with FOLFIRI in an exploratory analysis.[10] The PETACC-8 clinical trial randomized patients with stage III colon cancer to 6 months of FOLFOX4 chemotherapy with our without cetuximab.[9] Similar to N0147, the study was subsequently amended to include only patients with KRAS-WT tumors. No benefit from cetuximab was noted in terms of DFS in the KRAS-WT (HR 1.05; 95% CI, 0.85 to 1.29; $p = 0.66$) or in the KRAS/BRAF-WT (HR 0.99; 95% CI, 0.76 to 1.28; $p = 0.92$) populations. Interestingly, and in a preplanned subgroup analysis, patients with T4N2 tumors derived a significant benefit from the addition of cetuximab, whereas, women and patients with right colonic tumors experienced a significant improvement in DFS in the chemotherapy only arm.

Based on the N0147 and PETACC-8 studies, there is no current role for cetuximab in the adjuvant treatment of colon cancer. Although subgroup analyses of PETACC-8 suggest a benefit in more advanced T4N2 disease, this can be considered, at best, hypothesis generating. Clearly, a more predictive signature of response beyond RAS and BRAF mutations will be needed to revisit the role of anti-EGFR in the adjuvant treatment of mCRC. The reason for disconnect in benefits from anti-EGFR therapy between adjuvant and metastatic disease studies is not clear but could be explained by a failure to induce complete pathologic sterilization despite an increased antitumor down-staging in metastatic settings.

BIOLOGIC THERAPIES IN THE NEOADJUVANT TREATMENT OF MCRC
Biologic Therapies in the Neoadjuvant Treatment of Resectable mCRC

When considering neoadjuvant treatment in the management of metastatic colorectal cancer, one has to define the goal of therapy. The main indications for neoadjuvant treatment for metastatic colorectal cancer are: (1) decrease in the risk for recurrence of disease in the setting of resectable liver

metastases and (2) down-staging for resection in patients with potentially resectable disease. The EORTC 40983 study randomized patients with four or less hepatic colorectal metastases to perioperative FOLFOX chemotherapy or observation.[11] This study met its primary endpoint of 3-year DFS improvement in favor of FOLFOX. No significant improvement in OS was confirmed.[11,12] Since the EORTC control arm did not include postoperative chemotherapy, the benefits of perioperative chemotherapy compared with adjuvant postoperative chemotherapy are currently not substantiated.

Bevacizumab addition to neoadjuvant CAPOX, FOLFOX, FOLFIRI, and FOLFOXIRI has been shown to be feasible in patients with resectable liver mCRC.[13-15] Retrospective analyses suggest an increased likelihood of complete pathologic responses of liver metastases and a lower incidence of sinusoidal damage with the integration of bevacizumab in the preoperative chemotherapy treatment of liver mCRC.[16-18] However, there is no strong evidence to date to support an improvement in DFS or OS with the addition of bevacizumab to preoperative chemotherapy in these settings. Given the discouraging DFS and OS data with bevacizumab in stage III colorectal clinical trials, there is no strong rationale to incorporate bevacizumab in the neoadjuvant or postoperative therapy in patients with resectable mCRC. Indeed, a recent retrospective analysis of patients undergoing hepatectomy with adjuvant chemotherapy with or without bevacizumab failed to show any additional benefit in the bevacizumab arm.[19]

The role of cetuximab as part of a neoadjuvant chemotherapy regimen in resectable mCRC to the liver was investigated through the New EPOC trial.[20] In this randomized phase III clinical trial, patients with resectable or suboptimally resectable *KRAS*-WT metastatic colorectal cancer to the liver were randomly assigned to perioperative chemotherapy with or without cetuximab. The progression-free survival (PFS) was significantly shorter in the chemotherapy/cetuximab compared with the chemotherapy arm (14.1 vs. 20.5 months; HR 1.48; 95% CI, 1.04 to 2.12; p = 0.03). Chemotherapy consisted predominantly of oxaliplatin-based therapy (FOLFOX or XELOX), although, 11% of the patient population received FOLFIRI. Given the small number of patients on the irinotecan arm, no definitive conclusions can be extrapolated from this subgroup.[20] This study was criticized for lack of adequate surgical quality control, imbalance in patient characteristics, variations in chemotherapy backbones, and increased rate of early death without clear attribution.[21]

The detrimental effect of cetuximab on the New EPOC trial and the lack of benefit from adjuvant cetuximab treatment in stage III disease suggest that the addition of cetuximab to chemotherapy in *KRAS*-WT tumors does not improve the rate of microscopic disease eradication and, hence, does not decrease the risk for disease relapse. This strategy should be avoided in patients with resectable liver metastases.

Biologic Therapy in the Management of Potentially Resectable mCRC

Down-staging for resection in the setting of metastatic disease that is deemed unresectable at the time of presentation but potentially resectable after a major clinical response should be considered a standard approach. Patients who are converted to resectable disease with chemotherapy achieve a 5-year OS of 30% to 50%, far exceeding any 5-year survival reported with palliative chemotherapy.[22,23] Therefore, it is imperative that the most effective combination chemotherapy is considered in patients with advanced, potentially resectable, mCRC.

Since no randomized studies have evaluated the combination cytotoxic chemotherapy compared with cytotoxic chemotherapy/bevacizumab in such settings, one cannot conclusively determine the role of angiogenesis inhibition in down-staging for resection. However, since many of the patients with potentially-resectable disease do not achieve resectability, and given the positive effect of bevacizumab on PFS and OS, the routine implementation of bevacizumab in this setting is considered an acceptable practice, particularly when anti-EGFR therapy is not considered or advisable. Additional considerations for the addition of bevacizumab in this setting include retrospective analyses suggesting increased complete pathologic responses and decreased sinusoidal damage to the liver with the addition of bevacizumab to chemotherapy.[16-18] When considering bevacizumab in the management of potentially resectable mCRC, it is important to consider the most effective chemotherapy backbones. To that end, the OLIVIA clinical trial randomized patients with initially unresectable colorectal liver metastases to FOLFOX plus bevacizumab or FOLFOXIRI plus bevacizumab.[15] The FOLFOXIRI arm was associated with an improved response rate, a higher resection rate, higher R0 resection rate, and improved PFS (Table 1).

Although the addition of cetuximab to chemotherapy in the setting of resectable hepatic metastatic disease has resulted in disappointing results, the value of cetuximab in unresectable-potentially resectable hepatic metastatic disease has been supported by several studies. A phase III clinical trial randomized patients with *KRAS*-WT tumors with unresectable hepatic mCRC to receive first-line FOLFOX or FOLFOX/cetuximab.[24] Patients assigned cetuximab achieved a higher response rate, R0 hepatic resection rates, and OS (Table 1). Additional support to this strategy comes from several other phase II clinical trials describing a high response rate and resection rates with cetuximab-based combinations.[25,26] In addition, a recent update from CALGB 80405 reported that 15.7% of 1,137 patients with *KRAS*-WT tumors underwent resection after 1:1 randomization to chemotherapy with bevacizumab or chemotherapy plus cetuximab.[27] A higher percentage of patients underwent resection (with no evidence of disease) in the cetuximab arm in comparison with bevacizumab (62% vs. 38%). No OS difference in outcome was noted between arms after resection, suggesting that preoperative cetuximab does not worsen postoperative outlook when compared with a bevacizumab backbone (Table 1).

Both bevacizumab and cetuximab are justified in the setting of unresectable, potentially-resectable mCRC. Since the majority of these patients do not attain resectability, the integration of biologic therapy in the first-line setting is recom-

TABLE 1. Biologicals in Initially Non-Resectable CRC Liver Metastases

	Study Design	Treatment Arm	Comparator Arm	RR and Resection Rate	PFS/OS
Gruenberge et al[15] 2015	Randomized phase II clinical trial 80 patients Primary endpoint: overall resection rate	FOLFOX/BV	FOLFOXIRI/BV	Favors FOLFOXIRI arm RR: 81% vs. 62% Resection rate: 61% vs. 49% R0: 49% vs. 23%	Favors FOLFOXIRI arm PFS 18.6 vs. 11.5 months
Ye et al[24] 2013	Randomized phase III trial of 138 patients (*KRAS*-WT) Primary endpoint: conversion rate to radical resection	FOLFOX	FOLFOX/Cmab	Favors Cmab arm Resection rate: 29% vs. 13% R0: 26% vs. 7%	Favors Cmab arm PFS (HR 0.6, p = 0.04) OS (HR 0.54, p = 0.013)
Venook et al[27] 2014	Randomized phase III clinical trial Primary endpoint: OS 1,137 patients *KRAS*-WT (exon 2)	Chemotherapy/BV	Chemotherapy/Cmab	130 patients achieved surgical remission (favors Cmab arm) Cmab arm: 62% vs. 38%	No difference in OS between arms OS for overall patient population with surgical remission

Abbreviations: RR, response rate; PFS, median progression-free survival; OS, median overall survival; HR, hazard ratio; BV, bevacizumab; Cmab, cetuximab; WT, wild type.

mended in view of its positive effect on PFS and OS. In the setting of *RAS*-mutant type (MT) or *BRAF*-MT tumors, one would favor the use of FOLFOXIRI/bevacizumab in younger good performance status (PS) cases. In the setting where a doublet chemotherapy is chosen (more limited PS, older, etc.), an anti-EGFR addition is a reasonable choice in *RAS*-WT tumors given its more pronounced effect on downstaging compared with bevacizumab.

BIOLOGIC THERAPY IN NON-RESECTABLE MCRC

The choice of biologic therapies in mCRC is often considered in view of the genetic profile of the tumor. In this review, we will consider the pros and cons for angiogenesis targeting or EGFR targeting based on RAS and BRAF status.

Biologic Therapies in *RAS*-MT and *BRAF*-MT Tumors

Tumors with *RAS* mutations (exon 2, 3, and 4 of *KRAS* and *NRAS*) constitute approximately 50% of tumors; whereas, patients with *BRAF* mutations constitute 5% to 10% of patients with colorectal cancer.[28,29] Patients with *RAS*-MT tumors derive no benefit from the addition of anti-EGFR therapy to chemotherapy.[30] To the contrary, the addition of cetuximab to oxaliplatin-based chemotherapy has been associated with worsening in multiple outcome parameters.[28,29,31] The benefits of bevacizumab in mCRC have been shown to transcend *RAS* or *BRAF* mutational status and, therefore, the benefits reported on from phase III clinical trials from molecularly unselected patients with mCRC can be extrapolated to both *RAS*-WT and *RAS*-MT tumors.[32,33]

Targeted Therapy in the First-Line Treatment

The only angiogenesis-targeting agent to show improvement in PFS and OS in the first-line treatment of mCRC is bevacizumab. These studies were performed in *RAS* and *BRAF* unselected patients but can be extrapolated to the *RAS*-MT population.[32,33] The only phase III study to report a significant improvement in OS was the AVF2107 study. AVF2107 randomized patients to irinotecan and 5-FU/leucovorin with or without bevacizumab.[34] Subsequent first-line phase III

studies have consistently confirmed an advantage to the addition of bevacizumab to several fluoropyrimidine-based backbones, albeit with a PFS primary endpoint.[35-37] The advantage of the incorporation of bevacizumab in first-line treatment of mCRC has been particularly notable in the setting of fluoropyrimidine monotherapy.[37] The addition of bevacizumab to FOLFOX or XELOX has resulted in a clinically modest improvement in PFS and insignificant improvement in OS.[35] Given the favorable toxicity profile of bevacizumab and its reproducible positive effect on PFS, it is recommended that this agent is considered in the first-line treatment of patients with *RAS*-MT or *BRAF*-MT cancer (and as an option for *RAS*-WT as discussed below). Since anti-EGFR therapy is not an option in this setting, this is considered the only viable option for targeted therapy in this population. The reader is directed to our recent review on targeted therapy for further details on this topic.

There is no convincing evidence that patients with *BRAF*-MT mCRC derive a clinically significant benefit from anti-EGFR therapy.[35,38] Significant progress is being made through the concurrent targeting of EGFR and BRAF (with or without MEK) in this population.[39,40] However, such strategies are still considered investigational. Therefore, consideration of front-line addition of bevacizumab should be made in this subgroup of patients. However, the outlook of these patients continues to be dismal. Recent subgroup analysis from the TRIBE clinical trial has suggested a benefit from FOLFOXIRI/bevacizumab in comparison with FOLFIRI in patients with *BRAF*-MT disease.[1] Given the aggressive biology of *BRAF*-MT cancers, consideration for up-front FOLFOXIRI/bevacizumab should be considered in the younger fit individuals.

Targeted Therapy in the Second-Line Treatment

The value of bevacizumab in the second-line treatment of patients with previously bevacizumab-naive disease who progressed on a first-line therapy of irinotecan plus 5-FU has been confirmed through the ECOG 3200 clinical trial.[41] In this study, patients receiving FOLFOX/bevacizumab experienced a superior response rate, PFS, and OS than the

FOLFOX control arm (Table 2). However, in clinical practice, most patients who proceed to second-line treatment have had prior bevacizumab exposure. Three randomized phase III clinical trials have now reported on angiogenesis targeting post-bevacizumab progression.[41-43] The results of these studies are summarized in Table 2. Both the ML18147 and RAISE clinical trials mandated prior progression on a bevacizumab-based therapy and resulted in significant improvements in PFS and OS in favor of bevacizumab and ramucirumab.[44] The VELOUR clinical trial included both patients with bevacizumab-naive and bevacizumab pretreated disease and resulted in significant improvement in PFS and OS in the overall population. None of the three trials showed an improvement in response rate in the patients who were bevacizumab-pretreated. The three agents investigated are different biologically with bevacizumab being directed toward VEGF-A, aflibercept toward VEGF-A, VEGF-B and PlGF, and ramucirumab toward VEGFR-2. Although no head-to-head comparison among these agents have been performed to date, bevacizumab has been associated with the most favorable safety profile, whereas, concerns have been raised regarding the increased toxicity of aflibercept when combined with chemotherapy.[43] All three antiangiogenic agents are considered acceptable options for second-line treatment, with a preference toward bevacizumab given its more established safety profile. Although bevacizumab can be considered across different backbones in the second-line treatment, aflibercept and ramucirumab should only be considered with FOLFIRI. No clinical or biologic biomarkers have been identified to direct treatment toward any of these three biologicals in the setting of second-line FOLFIRI.

Targeted Therapy in Chemotherapy-Refractory or Resistant Colorectal Cancer

The CORRECT clinical trial[45] enrolled patients with mCRC who progressed after or were intolerant of fluoropyrimidines, oxaliplatin, irinotecan, and anti-EGFR therapy (in *KRAS*-WT). All patients had received prior bevacizumab. The study showed a significant clinically modest improvement in OS (median OS 6.4 vs. 5 months; HR 0.77; 95% CI, 0.64 to 0.94; one-sided p = 0.0052). Consideration for single-agent regorafenib can therefore be made after progression on all standard chemotherapy.

Biologic and Targeted Therapies in *RAS*-WT Tumors

It is important to note that the recommendations regarding antiangiogenesis therapies reported above for the *RAS* or *BRAF*-MT populations apply equally to the *RAS/BRAF*-WT population. On the other hand, the management of the *RAS/BRAF*-WT population is complicated by the proven effectiveness of anti-EGFR therapy across all lines of treatment. Therefore, treatment decisions in patients with *RAS/BRAF*-WT disease have to factor in efficacy and toxicity data with both classes of targeted agents. In this section we address the effect of anti-EGFR agents in this group of patients, and when feasible, put it in context of antiangiogenic therapies.

Targeted Therapies in the First-Line Treatment of *RAS*-WT mCRC

The CRYSTAL clinical trial evaluated the combination of FOLFIRI with cetuximab compared with FOLFIRI alone in the first-line treatment of mCRC.[46] No benefit was noted in the *KRAS*-MT (exon-2) population, whereas, a significant

TABLE 2. Angiogenesis Targeting in the Second-Line Treatment of mCRC

	Study Design	Control Arm	Experimental Arm	Efficacy Objectives	Primary Efficacy Endpoint	Other Efficacy Endpoints
Giantonio et al[41] ECOG 3200 study	Second-line randomized phase III clinical in BV-naive disease 829 patients	FOLFOX4	FOLFOX4/BV	Primary: OS Secondary: PFS, RR	OS: 12.9 (FOLFOX4/BV) vs. 10.8 months (FOLFOX4) (HR 0.75, p = 0.001)	PFS: 7.3 (FOLFOX4/BV) vs. 4.7 months (FOLFOX4) (HR 0.61, p < 0.0001) RR: 22.7% (FOLFOX4/BV) vs. 8.6% (FOLFOX4) (p < 0.0001)
Bennouna et al[44] ML18147 Study	Second-line randomized phase III clinical trial in patients post-BV first-line progression 820 patients	Chemotherapy	Chemotherapy/BV	Primary: OS Secondary: PFS, RR	OS: 11.2 (chemotherapy/BV) vs. 9.8 months (chemotherapy) (HR 0.81, p = 0.0062)	PFS: 5.7 (chemotherapy/BV) vs. 4.1 months (chemotherapy) (HR 0.68, p < 0.0001) No difference in RR
Van Cutsem et al[43] VELOUR Study	Second-line randomized phase III clinical trial 1,226 patients (70% of patients without prior BV)	FOLFIRI	FOLFIRI/ ziv-aflibercept	Primary: OS Secondary: PFS, RR	OS: 13.5 (FOLFIRI/ziv-aflibercept) vs. 12.06 months (FOLFIRI) (HR 0.817, p = 0.0032)	PFS: 6.9 (FOLFIRI/ziv-aflibercept) vs. 4.7 months (FOLFIRI) (HR 0.758, p < 0.0001) RR: 19.8% (FOLFIRI/ziv-aflibercept) vs. 11.1% (FOLFIRI) (p < 0.001) No difference in RR in patients with prior BV
Tabernero et al[42] RAISE Study	Second-line randomized phase III clinical trial in patients post-BV first-line progression 1,072 patients	FOLFIRI	FOLFIRI/RAM	Primary: OS Secondary: PFS, RR	OS: 13.3 (chemotherapy/RAM) vs. 11.7 months (chemotherapy) (HR 0.84, p = 0.00219)	PFS: 5.7 (chemotherapy/BV) vs. 4.5 months (chemotherapy) (HR 0.79, p < 0.0005) No difference in RR

Abbreviations: OS, overall survival; RR, response rate; PFS, progression-free survival; HR, hazard ratio; BV, bevacizumab; RAM, ramucirumab.

TABLE 3. EGFR Targeting in the First-Line Treatment of mCRC

	Study Design	Control Arm	Experimental Arm(s)	Efficacy Objectives	Primary Efficacy Endpoint	Other Efficacy Endpoints	
Maughan et al[29] COIN Study	Randomized phase III clinical trial (*KRAS*-WT for codons 12, 13, and 61) 815 patients per arm	Arm A: oxaliplatin/ fluoropyrimidine (FOLFOX or XELOX)	Arm B: oxaliplatin/ fluoropyrimidine/ Cmab	Primary: OS Secondary: RR, PFS	OS: 17 (Arm B) vs. 17.9 months (Arm A) (HR 1.04, p = 0.67) in the *KRAS*-WT population	PFS: 8.6 months (Arms A and B) (HR 0.96, p = 0.6) PFS HR for the FOLFOX arm favored Cmab (HR 0.72, p = 0.037)	
Tveit et al[48] NORDIC VII Study	Randomized phase III clinical trial 566 patients	FLOX (bolus 5-FU, leucovorin, and oxaliplatin) (Arm A)	FLOX/Cmab (Arm B)	Primary: PFS Secondary: RR, OS	*KRAS*-WT population: PFS: 7.9 (Arm B) vs. 8.6 months (Arm A) (HR 1.06, p = 0.66)	*KRAS*-WT population: RR: 49% (Arm B) vs. 41% (Arm A) (p = 0.15) No difference in OS (Arm A = 22 months, Arm B = 20.1 months)	
Douillard et al[28] PRIME study	Randomized phase III clinical trial 1,183 patients	FOLFOX4	FOLFOX4/Pmab	Primary: PFS Secondary: RR, OS	*KRAS* exon 2 WT: PFS: 9.6 (FOLFOX4/Pmab) vs. 8 months (FOLFOX4) (HR 0.8, p = 0.02) *RAS*-WT: PFS: 10.8 (FOLFOX4/Pmab) vs. 9.2 months (FOLFOX4) (HR 0.72, p = 0.004)	*KRAS* exon 2 WT: OS: 23.8 (FOLFOX4/Pmab) vs. 19.4 months (FOLFOX4) (HR 0.83, p = 0.03) *RAS*-WT: OS: 25.8 (FOLFOX4/Pmab) vs. 20.2 months (FOLFOX4) (HR 0.77, p = 0.009)	*KRAS* exon 2 WT: RR: 55% (FOLFOX4/Pmab) vs. 48% (FOLFOX4) (OR 1.35, p = 0.068)
Van Cutsem et al[46,47] CRYSTAL Study	Randomized phase III clinical trial 1,198 patients *KRAS* exon 2 WT: 676 patients	FOLFIRI	FOLFIRI/cetuximab	Primary: PFS Secondary: OS	*KRAS* exon 2 WT: PFS: 9.9 (FOLFIRI/Cmab) vs. 8.4 months (FOLFIRI) (HR 0.696, p = 0.0012) *RAS*-WT: PFS: 11.4 (FOLFIRI/Cmab) vs. 8.4 months (FOLFIRI) (HR 0.56, p = 0.0002)	KRAS exon 2 WT: OS: 23.5 (FOLFIRI/Cmab) vs. 20.2 months (FOLFIRI) (HR 0.797, p = 0.0093) *RAS*-WT: FOLFIRI/Cmab OS = 28.4 vs. FOLFIRI = 20.2 months (HR 0.69, p = 0.0024)	KRAS exon 2 WT: RR: 57.3% (FOLFIRI/Cmab) vs. 39.7% (FOLFIRI) (OR 2.069, p < 0.001) *RAS*-WT: FOLFIRI/Cmab RR = 66.3% vs. FOLFIRI = 38.6% (OR 3.11, p < 0.0001)

Abbreviations: mCRC, metastatic colorectal cancer; OS, overall survival; Cmab, cetuximab; Pmab, panitumumab; RR, response rate; PFS, progression-free survival; HR, hazard ratio; EGFR, epidermal growth factor receptor; OR, odds ratio; WT, wild type.

improvement in response rate, PFS, and OS was noted in the *KRAS*-WT subgroup.[46] Subsequent analysis based on *RAS*-WT (no *KRAS* or *NRAS* exon 2–4 mutations) showed even more robust improvements in PFS and OS than the *KRAS*-WT population (Table 3).[47] Similar benefits were noted with panitumumab with a FOLFOX backbone on the PRIME clinical trial (Table 3).[28] Two other phase III clinical trials failed to show a survival advantage for cetuximab in *KRAS*-WT tumors in the first-line setting (Table 3).[29,48] The NORDIC trial used a nonconventional bolus fluoropyrimidine-oxaliplatin regimen.[48] The COIN trial included XELOX as a chemotherapy backbone, which was associated with increased toxicities when combined with cetuximab and, therefore, potentially confounding cetuximab efficacy.[29] In addition, the lack of benefit on the NORDIC trial may have been confounded by a detrimental effect for cetuximab in the patients with *KRAS* (exon 3 and 4) and *NRAS* mutations who were included in the study analysis.

Three randomized first-line studies investigated bevacizumab compared with anti-EGFR therapy in the first-line treatment of *KRAS*-WT tumors (Table 4).[2,31,49] All three studies have reported efficacy data based on *RAS*-MT. The FIRE-3 and CALGB 80405 studies confirmed an improved response rate in favor of anti-EGFR therapy, no difference in PFS among arms, but diverted in the OS results. The FIRE-3 clinical trial showed an improvement in OS in *RAS*-WT tumors favoring cetuximab, whereas, no difference was noted in the CALGB 80405 study (Table 4).[2,49,50] The reason behind this difference in OS is unclear. A difference in postprogres-sion salvage rate with anti-EGFR therapy in the bevacizumab arms could very well have contributed to these variations in outcome. Other contributing factors could be variations in treatment compliance, dose intensity, and early treatment discontinuation because of toxicity, all of which are yet to be reported on CAALGB 80405. The PEAK clinical trial is a smaller randomized phase II clinical trial of FOLFOX/pani-tumumab compared with FOLFOX/bevacizumab.[31] The results from this study were somewhat consistent with the FIRE-3 clinical trial (Table 4). For further review, please refer to our recent review on this topic.

Both bevacizumab and anti-EGFR therapy are considered appropriate options in the first-line treatment of metastatic cancer. Given the increased down-staging potential of anti-EGFR therapy in the first-line setting compared with bevacizumab, this may be the more preferable biologic agent in the potentially resectable cases, especially when FOLFOXIRI (with or without bevacizumab) is contraindicated. In addition, anti-EGFR therapy is preferred in patients with higher risk for perforation (bulky primary, significant carcinomatosis) or with known risk factors for arterial thrombotic events. Bevacizumab is more preferable in patients who want to avoid skin toxicity.

Targeted Therapies in the Second-Line Treatment of *RAS*-WT mCRC

Although anti-EGFR therapy clearly increases the response rate and PFS in patients with *RAS*-WT mCRC, no studies have reported an improvement in OS in this setting (Table 5).[38,51,52] Two studies

TABLE 4. Anti-EGFR Versus Bevacizumab Plus Chemotherapy Studies in the First-Line Treatment of Metastatic Colorectal Cancer

Author/Study	Study Design	Control Arm	Experimental Arm(s)	Efficacy Objectives	Primary Efficacy Endpoint		Other Efficacy Endpoints	
Schwartzberg et al[31] PEAK Study	Randomized phase II clinical trial in *KRAS*-WT (exon 2) 285 patients	FOLFOX/BV	FOLFOX/Pmab	Primary: PFS Secondary: OS, RR	*KRAS*-WT PFS: 10.9 (Pmab) vs. 10.1 months (BV) (HR 0.87, p = 0.353)	*RAS*-WT PFS: 13 m (Pmab) vs. 9.5 months (BV) (HR 0.65, p = 0.029)	*KRAS*-WT RR: 57.8% (Pmab) vs. 53.5% (BV) OS: 34.2 (Pmab) vs. 24.3 months (BV) (HR 0.62, p = 0.009)	*RAS*-WT RR: 63.6% (Pmab) vs. 60.5% (BV) OS: 41.3 (Pmab) vs. 28.9 months (BV) (HR 0.63, p = 0.058)
Heinemann et al[49] Stintzing et al[50] FIRE-3 Study	Randomized phase III clinical trial in *KRAS*-WT WT (exon-2) 592 patients *RAS*-WT: 400 patients	FOLFIRI/BV	FOLFIRI/Cmab	Primary: RR Secondary: PFS, OS	*KRAS*-WT (independent review): RR: 66.5% (Cmab) vs. 55.6% (BV) (OR 1.58, p = 0.016) *RAS*-WT (independent review): RR: 72% (Cmab) vs. 56% (BV) (OR 2, p = 0.003)		*KRAS*-WT: OS: 28.7 (Cmab) vs. 25 months (BV) (HR 0.77, p = 0.017) PFS = 10 (Cmab) vs. 10.3 months (BV) (HR 1.06, p = 0.55) *RAS*-WT: OS: 33.1 (Cmab) vs. 25 months (BV) (HR 0.7, p = 0.0059) PFS = 10.3 (Cmab) vs. 10.2 months (BV) (HR 0.97, p = 0.77)	
Venook et al[2] Lenz et al[27] CALGB 80405	Randomized phase III clinical trial 1,137 patients *KRAS*-WT (exon 2) *RAS*-WT: 526 patients	(FOLFOX or FOLFRI)/BV	(FOLFOX or FOLFRI)/ Cmab	Primary: OS Secondary: PFS	*KRAS*-WT: OS: 29.9 (Cmab) vs. 29 months (BV) (HR 0.92, p = 0.3) *RAS*-WT: OS: 30.8 (Cmab) vs. 30.3 months (BV) (HR 0.9, p = 0.4)		*KRAS*-WT: RR: 65.6% (Cmab) vs. 57.2% (BV) (p = 0.002) *KRAS*-WT: PFS: 10.4 (Cmab) vs. 10.8 months (BV) (HR 1.04, p = 0.55)	*RAS*-WT: RR: 68.8% (cetuximab) vs. 56% (BV) (p < 0.001) *RAS*-WT: PFS: 10.9 (Cmab) vs. 11.4 m (BV) (HR 1.1, p = 0.31)

Abbreviations: EGFR, epidermal growth factor receptor; Pmab, panitumumab; Cmab, cetuximab; BV, bevacizumab; PFS, progression-free survival; OS, overall survival; RR, response rate; HR, hazard ratio; OR, odds ratio; WT, wild type.

evaluated cetuximab and panitumumab in the setting of single-agent irinotecan.[38,51] The EPIC trial did not select patients based on *RAS* status but reported improvements in response rate and PFS.[51] The PICCOLO study excluded patients with *KRAS* codon 12, 13, and 61 mutations and showed an improvement in response rate and PFS, but no benefit in OS.[38] The 20050181 study randomized patients to FOLFIRI plus panitumumab compared with FOLFIRI in patients with *KRAS* (exon-2) WT disease.[52] A significant improvement in response rate and PFS was noted on the panitumumab arm. A recent update on this study showed further accentuation of benefit in favor of panitumumab in the *RAS*-WT population (Table 5).[53]

It is unclear at this time what the best strategy is for a biologic therapy in the second-line setting of *RAS*-WT tumors after progression on first-line bevacizumab-based combinations. The continuation of bevacizumab or a switch to anti-EGFR– based therapy (in the setting of irinotecan-based backbone) is acceptable. However, in the setting where down-staging is important, anti-EGFR therapy is more appropriate.

Targeted Therapies in the Third-Line Treatment of *RAS*-WT mCRC

There is no current data to support the continuation of bevacizumab in the third-line treatment in mCRC. In patients who have progressed on all cytotoxic chemotherapies, the combination of anti-EGFR plus irinotecan is considered the most appropriate choice in patients with good PS who are irinotecan tolerant.[54] The use of cetuximab or panitumumab monotherapy in this setting is also considered appropriate based on the C017 and the ASPECCT trials (Table 6).[55,56] Regorafenib should only be considered after failure (or intoler-

TABLE 5. EGFR Targeting in the Second-Line Treatment in *KRAS*-WT Metastatic Colorectal Cancer

	Study Design	Control Arm	Experimental Arm(s)	Efficacy Objectives	Primary Efficacy Endpoint	Other Efficacy Endpoints	
Peeters et al[52] 20050181 Study	Second-line randomized phase III clinical trial *KRAS* exon 2 WT: 597 patients	FOLFIRI	FOLFIRI + Pmab	Primary: PFS Secondary: OS	PFS: 5.9 m (FOLFIRI + Pmab) versus 3.9 m (FOLFIRI) (HR = 0.73, p = 0.004)	OS: 14.5 m (FOLFIRI + Pmab) versus 12.5 m (FOLFIRI) (HR = 0.85, p = 0.12)	RR: 35% (FOLFIRI + Pmab) versus 10% (FOLFIRI) (p < 0.001)
Seymour et al[38] PICOLLO Study	Second-line randomized phase III clinical trial *KRAS* WT (codon 12, 13, 61) = 460 allocated to irinotecan with or without panitumumab	Irinotecan 300 mg/m² to 350 mg/m² every 3 weeks	Irinotecan/panitumumab (9 mg/kg every 3 weeks)	Primary: OS Secondary: PFS, RR	OS: 10.4 (irinotecan/ Pmab) vs. 10.9 months (irinotecan) (HR 1.01, p = 0.91)	PFS: Pmab/irinotecan arm was superior to irinotecan (HR 0.78, p = 0.015)	RR: 33% (Pmab/irinotecan) vs. 12% (irinotecan) (OR 4.12, p < 0.0001)

Abbreviations: EGFR, epidermal growth factor receptor; OS, overall survival; RR, response rate; PFS, progression-free survival; HR, hazard ratio; OR, odds ratio; WT, wild type.

TABLE 6. EGFR Targeting in Chemotherapy Resistant *KRAS*-WT mCRC

	Study Design	Control Arm	Experimental Arm(s)	Efficacy Objectives	Primary Efficacy Endpoint	Other Efficacy Endpoints
Karapetis et al[56] NCI-CO17 Study	Randomized phase III clinical trial *KRAS*-WT (exon 2), 230 patients	BSC	Cmab	Primary: OS Secondary: PFS, RR	OS: 9.5 (Cmab) vs. 4.8 months (BSC) (HR 0.55, p < 0.001)	PFS: 3.7 (Cmab) vs. 1.9 months (BSC) (HR 0.40, p < 0.001) RR: 12.8% (Cmab) vs. 0% (BSC)
Price et al[55] ASPECCT Study	Randomized phase III non-inferiority clinical trial in patients with *KRAS*-WT 1,010 patients	Cmab	Pmab	Primary: OS Secondary: PFS, RR	OS: 10.4 (Pmab) vs. 10 months (Cmab) Pmab non-inferior to Cmab	PFS: 4.1 (Pmab) vs. 4.4 months (Cmab) (HR 1.0; 85% CI, 0.88 to 1.14) RR: 22% (Pmab) vs. 19.8% (Cmab)

Abbreviations: mCRC, metastatic colorectal cancer; OS, overall survival; RR, response rate; PFS, progression-free survival; HR, hazard ratio; EGFR, epidermal growth factor receptor; Cmab, cetuximab; Pmab, panitumumab; OR, odds ratio; BSC, best supportive care; WT, wild type.

ance) of all cytotoxic and anti-EGFR therapy. It is important to note that no randomized data have reported on anti-EGFR recycling and that the above recommendations in the second- and third-line treatment with anti-EGFR therapy are based on clinical trials of patients with anti-EGFR naive disease. The question of recycling is an important research question given the *RAS*-mutation emergence in the setting of anti-EGFR therapy. It is possible that prolonged breaks after anti-EGFR progression allow for tumor reconstitution with anti-EGFR sensitive clones resulting in further benefit from anti-EGFR rechallenge. A small phase II clinical trial supports this concept; however, more studies are needed to confirm these findings and to identify the patients who would best benefit from this strategy.[57]

Disclosures of Potential Conflicts of Interest

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Systemic Treatment: Maintenance Compared with Holiday

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OVERVIEW

With the currently available cytotoxic and targeted drugs, metastatic colorectal cancer (mCRC) may be controlled by systemic treatment for a substantial period of time. However, many questions remain about the optimal use of drugs and duration of treatment. The feasibility of chemotherapy-free intervals has been studied in patients with mCRC treated with chemotherapy alone, but the results are conflicting. Current data show that oxaliplatin may be safely interrupted, but they do not allow a firm conclusion on the safety of a full treatment break of chemotherapy. For targeted therapy, continuous inhibition of intracellular signaling by prolonged administration would theoretically be beneficial for efficacy of treatment. Recent data support the use of maintenance treatment with chemotherapy and bevacizumab. No data on the optimal duration of treatment with anti-epidermal growth factor receptor (EGFR) agents are currently available.

Colorectal cancer is the second most common cause of cancer deaths worldwide, and its incidence is still increasing. Approximately 50% of the patients will eventually develop distant metastases, which may be treated with surgical resection and/or systemic treatment. The systemic treatment for mCRC has changed substantially over the past 20 years. Currently available drugs with proven efficacy can be classified as cytotoxic (i.e., classic chemotherapy) and targeted drugs (e.g., antibodies, small molecules). A large number of patients respond well to treatment, and many patients often ask for drug holidays. If this would not compromise survival, a drug holiday could increase quality of life (QoL) and would reduce health care costs. This paper will review the data on the optimal duration of treatment.[1]

CHEMOTHERAPY

Effective cytotoxic drugs in mCRC include the fluoropyrimidines, irinotecan, and oxaliplatin. These drugs are the backbone of systemic treatment of mCRC. There is no outright preference for either oxaliplatin or irinotecan in first-line combination schedules.[2] Retrospective studies have shown that the exposure to these three cytotoxics during the course of disease appears more important than their up-front combined use.[3-5] This has been confirmed by the results of subsequent prospective studies, of which the results showed no benefit for up-front combination treatment over sequential treatment starting with fluoropyrimidine monotherapy.[6,7] The choice between combination or sequential therapy may depend on several factors, such as tumor-related symptoms, potential resectability of metastases, and performance sta-

tus.[8] As a result of the improved outcome of treatment, an increasing number of patients continue to do well on chemotherapy. Objective responses are usually achieved within the first 4 to 6 months of treatment.

Optimal Duration of Chemotherapy

The optimal duration of treatment is still a matter of debate, with no consensus on whether chemotherapy should be continued until disease progression or that a chemotherapy break is justified after the maximum response has been achieved. Furthermore, in case of intermittent treatment, it is unknown whether treatment should be resumed after a predefined interval or at disease progression. The feasibility of chemotherapy-free intervals has been studied, but the results are conflicting. In a Medical Research Council study, patients with stable disease or better after initial 12 weeks of chemotherapy were randomly selected to receive continuous or intermittent treatment, with resumption of the initial treatment on progression.[9] No survival difference was observed between the continuous and intermittent treatment arm. However, a large number of eligible patients refused to be randomly assigned or received unplanned treatment on progression. The availability of oxaliplatin introduced the problem of handling its most relevant toxic effect: the sensory neuropathy. The question arose whether intermittent treatment with oxaliplatin could reduce neurotoxicity without a detrimental effect on efficacy. The OPTIMOX1 study randomly selected previously untreated patients with mCRC to receive oxaliplatin in combination with 5-fluorouracil (5-FU)/leucovorin (LV; FOLFOX4) until progression or six cycles of FOLFOX7, followed by maintenance treatment with

5-FU/LV for 12 cycles and then reintroduction of FOLFOX7 until progression.[10] There was no significant difference in median progression-free survival (9.0 vs. 8.7 months, hazard ratio [HR] 1.06, p = 0.47) or overall survival (19.3 vs. 21.2 months, HR 0.93, p = 0.49). In the intermittent treatment arm, a decreased incidence of toxicity was observed. Oxaliplatin was reintroduced in this treatment arm in 40% of the patients, in whom disease control was achieved in 70%. The authors concluded that oxaliplatin can be safely discontinued after six cycles. Next, the OPTIMOX2 trial was conducted to evaluate the strategy of discontinuation of all oxaliplatin-based chemotherapy compared with maintenance with 5-FU/LV after induction treatment with FOLFOX7.[11] In both arms, FOLFOX was reintroduced on disease progression, which, different from RECIST criteria, was defined as the time point at which tumors had regained their initial pretreatment size. The median progression-free survival was significantly prolonged in the maintenance arm as compared to the chemotherapy-free interval arm (8.6 vs. 6.6 months, respectively; HR 0.61, p = 0.017), but there was no significant difference in median overall survival (23.8 vs. 19.5 months; HR 0.88, p = 0.42). However, the trial was discontinued early because of the registration of bevacizumab, and therefore, no definite conclusions could be drawn. QoL was not evaluated in either OPTIMOX1 or OPTIMOX2.

The COIN trial also investigated intermittent compared with continuous chemotherapy.[12] Patients were randomly assigned to continuous oxaliplatin plus 5-FU/LV (FOLFOX) or capecitabine (CAPOX) or the same regimen given for 12 weeks with resumption of treatment on disease progression. Patients on intermittent treatment did spend less time on treatment, had substantially less toxicity, and scored better on several QoL symptom scales (but not on QoL global scales). Median overall survival in the continuous and the intermittent group was 15.8 and 14.4 months, respectively (HR 1.08, p = 0.60). Patients with elevated baseline platelet counts did perform poorly on intermittent treatment. The authors concluded that although noninferiority was not shown for intermittent treatment, chemotherapy-free intervals may be a treatment option for selected patients.

For irinotecan-based chemotherapy, two studies investigated whether continuous treatment was superior to a defined period of treatment. In a study by Lal et al, patients with stable disease or better after eight cycles of irinotecan in second line were randomly assigned to continuation or discontinuation of irinotecan until disease progression.[13] Only 17% of the patients who received second-line irinotecan were eligible for randomization, leaving 55 evaluable patients. There was no difference in median progression-free survival or overall survival between the two treatment arms. Furthermore, QoL was comparable in both arms. Although these results suggest that irinotecan can be safely discontinued after eight cycles, this study was underpowered. In the GISCAD study,[14] a total of 337 patients were randomly selected to receive intermittent treatment with FOLFIRI given in a 2-months-on 2-months-off schedule or continuous treatment with FOLFIRI—both until disease progression. The intermittent schedule was not inferior to continuous treatment for the primary endpoint of overall survival nor for progression-free survival or response rate. Furthermore, toxicity profiles were comparable, which is not surprising, as the toxicities of irinotecan are usually not cumulative. QoL was not evaluated in this study. The authors concluded that the intermittent use of FOLFIRI does not decrease its efficacy compared to its continued use.

These data show that QoL has been investigated in only a few studies that address the benefit of intermittent compared with continuous treatment. Although palliative chemotherapy by definition should primarily strive for the relief or the delay of symptoms, it has been shown that patients' main incentive to accept palliative chemotherapy in advanced CRC trials is prolongation of life rather than improvement of QoL.[15,16] With the observed small or absent differences between the treatment strategies in the aforementioned trials, data on QoL would therefore be helpful to discuss these strategies with patients.

TARGETED THERAPY

Targeted drugs with efficacy in mCRC include bevacizumab—an antibody against vascular endothelial growth factor A (VEGF)—and cetuximab and panitumumab—antibodies against the EGFR.[17] More recently, aflibercept—a recombinant fusion protein that blocks the activity of VEGF and placental growth factor[18]—and regorafenib—a multikinase inhibitor that blocks the activity of several protein kinases involved in tumor angiogenesis, oncogenesis, and the tumor microenvironment— have shown efficacy in patients with mCRC.[19] Bevacizumab and aflibercept are used in combination with chemotherapy, and the anti-EGFR antibodies may also be used as monotherapy. The currently available data support use of regorafenib only as monotherapy. Bevacizumab has shown survival benefits with fluoropyrimidine-containing chemotherapy and is currently considered as a standard first-line treatment option for patients with mCRC.[20-24] In second line, bevacizumab also improved progression-free survival and overall survival in combination with FOLFOX chemotherapy.[25] This latter study showed no benefit for bevacizumab monotherapy. The benefit of the anti-EGFR antibodies panitumumab and cetuximab is restricted to patients with a *RAS* wild-type tumor.[26] These antibodies have shown survival benefits with chemotherapy in first line[27-29] and

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KEY POINTS

- Maintenance treatment with capecitabine plus bevacizumab is effective.
- Current data do not support the use of bevacizumab monotherapy.
- The optimal treatment duration of anti-EGFR therapy is unknown.
- For chemotherapy, current data do not allow a firm conclusion on the safety of a full treatment break.
- Oxaliplatin can be safely discontinued and re-introduced at progression of disease.

second line,[30] as well as monotherapy in late line.[31,32] Bevacizumab should not be combined with an anti-EGFR antibody.[33,34] In patients with *RAS* wild-type tumors, there appears no outright benefit for either bevacizumab or anti-EGFR antibody treatment in combination with first-line chemotherapy, although some studies show a yet unexplained survival benefit for starting with anti-EGFR treatment.[35-37] Aflibercept has shown efficacy in combination with FOLFIRI for patients with mCRC previously treated with an oxaliplatin-containing regimen, with or without bevacizumab.[18] For patients with mCRC whose disease progressed on these standard therapies, regorafenib increased overall survival compared with best supportive care.[19]

Optimal Duration of Targeted Therapy

Targeted therapy is characterized by the inhibition of intracellular signal transduction pathways that are relevant for tumor growth. RECIST criteria appear to be less suitable to evaluate its effects.[38,39] Theoretically, discontinuation of a drug that inhibits growth signals could result in tumor regrowth. This would favor its prolonged administration, which is, however, associated with a higher risk for toxicity and increased health care costs. The first data that supported the prolonged use of bevacizumab came from the NO16966 study.[22] In this study, first-line bevacizumab in combination with oxaliplatin-based chemotherapy showed only a modest increase in the primary endpoint of progression-free survival compared to chemotherapy alone (9.4 vs. 8.0 months; HR 0.83, p = 0.0023). However, compared to the initial registration study,[20] in the NO16966 study, a much lower percentage of patients received bevacizumab until disease progression or death. The relevance of this was shown by the results of a planned subset analysis of NO16966, taking into account only progression or death events occurring within 28 days from the last dose of any component of the study. In this analysis, the results of the chemotherapy-alone treatment were comparable with the overall analysis, but the median progression-free survival for chemotherapy plus bevacizumab was increased (HR 0.63). Further support for the benefit of prolonged use of bevacizumab comes from observational studies in which investigators could decide whether or not to continue bevacizumab after disease progression on first-line treatment, with a switch in the chemotherapy regimen.[40] Patients who continued bevacizumab beyond progression had increased overall survival. In an experimental model, bevacizumab beyond progression resulted in measurable changes in the tumor proliferation and microenvironment compared to discontinuation of bevacizumab.[41] The clinical observation was confirmed, albeit with a smaller benefit, in a prospective randomized study.[42] In this study, patients with mCRC with disease progression up to 3 months after discontinuing first-line chemotherapy plus bevacizumab were randomly assigned to second-line chemotherapy with or without bevacizumab. Median overall survival (primary endpoint) was significantly better in patients treated with bevacizumab (HR 0.81, p = 0.0062). The MACRO trial prospectively investigated the use of maintenance treatment of bevacizumab monotherapy in first line.[43] After six cycles of capecitabine, oxaliplatin, and bevacizumab, patients were randomly selected to receive either the continuous administration of this schedule or bevacizumab monotherapy. Noninferiority was not confirmed. The primary endpoint—median progression-free survival—was 10.4 compared with 9.7 months for the continuous and the monotherapy bevacizumab arm, respectively (HR 1.10, p = 0.38). Of note, patients were randomly selected at the start of first-line treatment, and therefore, the inclusion of patients who did not complete the first six cycles of induction therapy may have influenced the outcome. Furthermore, the efficacy of bevacizumab monotherapy may be questioned.[25,44] The SAKK 41/06 study assessed the efficacy of continuing treatment with single-agent bevacizumab after induction therapy with chemotherapy and bevacizumab.[45] In this phase III trial, patients with mCRC without disease progression after 4 to 6 months of standard first-line chemotherapy plus bevacizumab were randomly assigned to bevacizumab monotherapy or observation. Noninferiority of the primary endpoint time to progression (TTP) could not be demonstrated for treatment holidays compared with continuation of bevacizumab. Median TTP was 4.1 months for bevacizumab continuation compared with 2.9 months for no continuation (HR 0.74; 95% CI, 0.58 to 0.96). There was no difference in median OS between the treatment arms (HR 0.83, p = 0.2).

The CAIRO3 study of the Dutch Colorectal Cancer Group provided prospectively collected data on the optimal duration of treatment with chemotherapy and bevacizumab.[46] This study randomly selected patients with stable disease or better after six cycles of initial therapy to receive capecitabine, oxaliplatin, and bevacizumab and observation or maintenance therapy with continuous low-dose capecitabine and bevacizumab. Maintenance treatment significantly improved the first TTP (HR 0.43, p < 0.0001), the second TTP (primary endpoint) after reintroduction of capecitabine, oxaliplatin, and bevacizumab (HR 0.67, p < 0.0001), and the second TTP after any treatment following first progression (HR 0.68, p < 0.001). Toxicity of maintenance treatment was acceptable, and QoL did not deteriorate. Median overall survival was also improved by 3.5 months with maintenance treatment, but this was not statistically significant (HR 0.83, p = 0.06). However, the trial was not powered to demonstrate a benefit in overall survival. Notable survival benefits were observed in selected patient subgroups (e.g., patients with a complete or partial response as best response to induction treatment, and patients with synchronous metastatic disease and resected primary tumor). The main conclusion of CAIRO3 is that maintenance treatment with capecitabine plus bevacizumab is effective. The AIO 207 trial compared (1) maintenance treatment with a fluoropyrimidine plus bevacizumab, (2) bevacizumab alone, and (3) observation after induction treatment of 6 months with a fluoropyrimidine, oxaliplatin, and bevacizumab.[47] Maintenance treatment with bevacizumab alone was noninferior compared to chemotherapy plus bevacizumab for the primary endpoint: time to failure of treatment strategy. Noninferiority could not be demonstrated for no treatment. The main characteristics of

TABLE 1. Main Differences in Design of CAIRO3 and AIO 207 Trials

	CAIRO3	AIO 207
Patients	556	476
Design	Two-arm superiority	Three-arm noninferiority
Primary Endpoint	PFS2	TFS
Treatment Period Prior to Randomization	4.5 mo	6 mo
Exclusion of Patients Who Did Not Tolerate (Part of) Induction Treatment	Yes	No
Reintroduction of Oxaliplatin (%)	47%-60%	21%-45%

Abbreviations: PFS2, progression-free survival as measured by disease progression or death after reintroduction of capecitabine, oxaliplatin, and bevacizumab following either maintenance treatment with capecitabine plus bevacizumab or observation; TFS, time to failure of strategy, progression, or death after reintroduction of fluoropyrimidine, oxaliplatin, and bevacizumab following either maintenance treatment with fluoropyrimidine plus bevacizumab, bevacizumab alone, or observation.

CAIRO3 and AIO 207 are shown in Table 1. Although the design of AIO 207 was less straightforward than CAIRO3, the AIO 207 data support the use of fluoropyrimidine plus bevacizumab maintenance treatment.

For anti-EGFR treatment, only data from the NORDIC trial provide some insight on its optimal duration of treatment. This trial investigated treatment with first-line cetuximab with continuous or intermittent chemotherapy (fluorouracil, leucovorin, and oxaliplatin [FLOX]) compared with FLOX alone.[48] Cetuximab did not add a notable benefit to FLOX chemotherapy, neither given continuously nor given intermittently. No difference was found within subsets of patients with KRAS wild-type or mutant tumors; however, the study was not sufficiently powered for these subgroup analyses. The GERCOR DREAM study showed positive results for maintenance treatment with erlotinib—an EGFR tyrosine kinase inhibitor—in combination with bevacizumab.[49] After initial treatment with chemotherapy (FOLFOX, CAPOX, or FOLFIRI) and bevacizumab, patients with mCRC were randomly assigned to maintenance treatment with bevacizumab with or without erlotinib. The primary endpoint was progression-free survival on maintenance treatment, which was significantly better for patients treated with both drugs. However, the absolute benefit in median progression-free survival was only 1.1 month (HR 0.76, p = 0.010). Median OS was also significantly better for patients treated with maintenance treatment with bevacizumab plus erlotinib compared to bevacizumab monotherapy, 24.9 compared with 22.1 months, respectively (HR 0.79, p = 0.035). The NORDIC ACT trial had a similar design, randomly selecting patients to receive maintenance treatment with bevacizumab with or without erlotinib after induction treatment with chemotherapy (CAPIRI, CAPOX, FOLFIRI, OR FOLFOX).[50] The primary endpoint progression-free survival was not significantly different between the two arms, 5.7 compared with 4.2 months, respectively (HR 0.79, p = 0.12). Also median overall survival was comparable in both arms (HR 0.88, p = 0.51). Given the fact that the value of erlotinib has not been demonstrated in mCRC and that the efficacy of bevacizumab monotherapy is not supported by results of other trials, the implications of the DREAM and NORDIC ACT trial results for general practice are difficult to assess.

CONCLUSION

For the palliative treatment of patients with mCRC with chemotherapy alone, current data do not allow a firm conclusion on the safety of a full treatment break. The benefit of a drug holiday with a possible detrimental effect on outcome must be weighed against the toxicity and possibly decreased QoL that is associated with continuous treatment. In case of the use of combination chemotherapy with oxaliplatin, the chemotherapy may be reduced to fluoropyrimidine monotherapy during the maintenance phase, with reintroduction of oxaliplatin on progression. As to the use of targeted therapy, current data do not support the use of maintenance treatment with bevacizumab monotherapy. No data are available on the optimal duration of anti-EGFR antibody treatment. Data from the CAIRO3 and AIO 207 study support the use of maintenance treatment with chemotherapy and bevacizumab. Therefore, with bevacizumab being part of standard first-line treatment schedules, current data support the use of maintenance treatment with bevacizumab in combination with chemotherapy. Further studies should provide data on specific subgroups in which maintenance treatment is most effective.

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GASTROINTESTINAL (COLORECTAL) CANCER

Treatment of Colorectal Cancer Peritoneal Carcinomatosis: The Role of Surgery, Systemic, and Heated Intraperitoneal Chemotherapy

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Treatment of Peritoneal Carcinomatosis of Colorectal Origin

Andrea Cercek, MD, James C. Cusack Jr, MD, and David P. Ryan, MD

OVERVIEW

The management of peritoneal carcinomatosis from colon cancer remains a controversial issue. Peritoneal carcinomatosis is associated with worse survival and has led to an aggressive treatment that combines surgery and intraperitoneal chemotherapy (IPC). This review will describe the rationale behind this treatment and the current controversy surrounding it.

Metastatic colon cancer is generally considered incurable except for the setting of metastases that are isolated to the liver or lung and can be resected. During the last 20 years, there has been a marked improvement in the survival of patients with metastatic colon cancer because of the development of multiple anticancer drugs such as irinotecan, oxaliplatin, antivascular endothelial growth factor therapy, and anti-epidermal growth factor receptor therapy. When fluorouracil (5-FU) was the only available chemotherapy, the median survival and 5-year survival were 12 months and 1%, respectively.[1] With the advent of combination chemotherapy and multiple lines of therapy, the median survival is now approximately 2 years and the 5-year survival is greater than 20%.[2] Moreover, for those patients with disease isolated to the liver or lung that can be surgically resected, 20% to 40% of patients can be cured by complete resection of these metastases.

METASTATIC COLORECTAL CANCER AND PERITONEAL CARCINOMATOSIS

Peritoneal carcinomatosis is regarded by the patient and physician as one of the most feared ways that colon cancer metastasizes. From a patient's perspective, the presence of peritoneal metastases is not considered curable unlike resectable liver or lung metastases. Additionally, the presence of peritoneal carcinomatosis is associated with a worse overall survival compared with patients who lack any peritoneal carcinomatosis.[3] Additionally, peritoneal carcinomatosis is associated with a high symptom burden including nausea, vomiting, abdominal pain, bloating, and intestinal obstruction. From the doctor's perspective, these symptoms are often very difficult to control because of carcinomatosis and lead to frequent hospitalizations.[4] The degree of symptom burden often precludes the use of standard chemotherapy regimens because of the poor performance status of the patient.[5]

In response to these challenges, investigators have attempted to treat patients with isolated peritoneal carcinomatosis using cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). Earlier studies estimated that peritoneal carcinomatosis occurs as the sole site of disease in as many as 25% of patients, but a recent study evaluating the subset of patients with peritoneal carcinomatosis in the North Central Cancer Treatment Group studies 9741 and 9841 demonstrated that 17% of patients (364 of 2,101) enrolled in these two studies had peritoneal carcinomatosis as a component of multisite disease, and only 2.1% of patients (44 of 2,101) had peritoneal carcinomatosis as the sole site of disease.[3] Although the topic of CRS and HIPEC is often debated, the applicability to the management of metastatic colon cancer is uncommon.

CYTOREDUCTIVE SURGERY AND INTRAPERITONEAL CHEMOTHERAPY

CRS was introduced with the goal of removing all gross disease and, thus, prolonging survival.[6] CRS involves surgical resection of visible disease in the abdomen and pelvis (including visceral organs if involved by tumor). The extent of disease is assessed at initial exploration by the surgeon using a peritoneal cancer index (PCI), as initially described by Sugarbaker et al.[7] The abdominal cavity is divided into a grid of nine squares and the small bowel mesentery is separated into four quadrants; each grid or quadrant is scored, based on disease burden, on a scale of zero (no gross disease) to three (extensive disease). Therefore, the extent of disease can range from zero to 39; patients with a PCI of greater than 30 are generally thought to have a low likelihood of having a complete gross cytoreduction. After cytoreduction, a completeness of cytoreduction score (CCR) is then assigned. A CCR of zero signifies that no gross disease remains after CRS, whereas,

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a score of one indicates that tumor nodules remain but are all 2.5 mm or less in diameter. Residual disease that is greater than 2.5 mm in diameter is assigned a CCR of two or three depending on the size and extent of the tumor left behind. Cytoreduction is considered to be therapeutic when a CCR of zero or one is obtained, and has been shown to be independently associated with improved survival.[8] However, even with optimal cytoreduction, microscopic disease may be left behind. IPC was, therefore, developed to deliver regional chemotherapy into the peritoneal cavity, thereby attempting to eradicate the remaining microscopic disease.

The initial use of IPC was delivered in the postoperative setting and is known as EPIC (early postoperative IPC). In this approach, a catheter is placed intraoperatively and chemotherapy is administered into the peritoneum on several subsequent postoperative days. The drug most commonly used is floxuridine, which is a fluorinated pyrimidine analog of 5-FU. Although initial reports were promising, there were theoretical concerns of EPIC being unable to perfuse all peritoneal surfaces because of the onset of fibrosis and adhesions. Indeed, after a few cycles, many patients developed nausea, abdominal distension, and pain thought to be related to adhesions.

The advantage of IPC is that it enables the delivery of much higher doses of chemotherapy directly to the cancer cells than could be achieved systemically. First pass hepatic extraction of floxuridine is high, and, thus, high concentrations of floxuridine can be delivered into the peritoneum without substantial systemic absorption and toxicity.[8] For these reasons, many centers have explored and utilized IPC with EPIC after CRS since the early 1990s. To date, however, there are no randomized clinical trials that support its benefit.[9]

In an attempt to improve upon delivery of IPC, intraoperative delivery of heated chemotherapy was developed. HIPEC offers several theoretical advantages. First, it is given during the time of surgery, which minimizes the risk for adhesions. Second, the heated chemotherapy is thought to have

increased cytotoxicity based on animal and preclinical data.[10-12] Of note, a recent study using a rat model showed no benefit to HIPEC.[13]

There were two randomized studies of HIPEC compared with systemic chemotherapy. In the first, Verwall and colleagues randomly assigned 105 patients younger than age 71 to CRS plus HIPEC (using mitomycin C) or systemic therapy (using 5-FU/leucovorin) alone. The patients treated with CRS plus HIPEC had an improved median survival of 22.4 months compared with 12.6 months (p = 0.032).[14] Unfortunately, this study was conducted in the era of 5-FU therapy alone. The incremental survival benefit of 10 months is equivalent to what would be expected with modern systemic chemotherapy using oxaliplatin and irinotecan. Furthermore, the patients were not stratified based on prior 5-FU exposure, so it is not known whether they benefitted or progressed on 5-FU alone. Of the 105 patients, 18 (17%) had appendiceal tumors, which have variable histologies and can at times be more indolent than typical colorectal adenocarcinomas. Second- or third-line chemotherapy with oxaliplatin or irinotecan was not recorded, thus, we cannot learn if these subsequent regimens had an effect on outcome. Additionally, an important difference is noted between median survival of patients in the surgical arm between those who had limited peritoneal disease (29 months) and those with extensive disease (5 months). In the surgical group, 8% of patients died from postoperative complications. In a follow-up publication by Verwall et al with a median follow-up of 8 years, four out of 51 patients were alive in the systemic arm and five out of 54 in the CRS plus HIPEC arm.[15]

The second randomized study was attempted by the French group, Elias and colleagues. Unfortunately, it was terminated early before reaching the target accrual of 90 patients because of poor accrual. Thirty-five patients were randomly selected to receive CRS plus EPIC or CRS alone. EPIC did not appear to improve outcomes, but patients with CCR0 had a 60% 2-year survival.[16]

There are no randomized trials comparing HIPEC with EPIC. Elias et al reported a large retrospective cohort study of 523 patients from 23 centers who were treated with CRS and either HIPEC or EPIC.[17] The median survival was 30.1 months. The overall 1-year, 3-year, and 5-year survival rates were 81%, 41%, and 27%, respectively with a median follow-up of 45 months. The rate of grade 3 to 4 complications was 31% and the death rate was 3.3%. Multivariate analyses revealed that the only factor that correlated significantly with overall survival was the PCI index (p < 0.0001). The use of adjuvant systemic chemotherapy and lymph node status (p = 0.02) were noted but did not reach statistical significance.

In a systematic review of CRS IPC studies and case reports before March 2006, Yan and colleagues reported that 5-year survival rates varied from 11% to 19%. Patients who received complete cytoreduction benefitted most with median survivals between 28 months to 60 months and 5-year survival ranging from 23% to 44%.[18] Interestingly, Chua and col-

KEY POINTS

- Isolated peritoneal carcinomatosis related to colorectal cancer occurs infrequently and is associated with a poor prognosis.
- Therapeutic cytoreduction may be achieved using systemic chemotherapy and/or cytoredcutive surgery (CRS) and intraperitoneal heated chemotherapy (HIPEC).
- Optimal management of peritoneal carcinomatosis is determined by a multidisciplinary care team (medical oncologist and surgeon).
- Stringent selection criteria for patients undergoing CRS/HIPEC may reduce associated morbidity and mortality.
- The timing of CRS/HIPEC should be coordinated by the multidisciplinary care team.

leagues performed a meta-analysis of all CRS HIPEC cases performed between 1995 to 2009. In patients with complete cytoreduction (722 patients) the median overall survival was 33 months (range, 20 months to 63 months) and the median 5-year survival rate was 43% (range 20% to 51%).[19] In contrast, the patients with incomplete cytoreduction had a much poorer outcome with a median overall survival of only 8 months and a 5-year survival of 0%. These findings strongly suggest that appropriate patient selection is key in the success of CRS and IPC.

It is evident that surgically rendering patients free of all disease is associated with an increased chance of cure for patients with isolated liver or lung metastases. Therefore, it is reasonable to conjecture that some patients with isolated and/or limited peritoneal metastases can be resected for cure. Although the surgical series suggest that this may be the case, it is difficult to tease out the independent effects of CRS from IPC since they are given concurrently. A well-designed multicenter randomized controlled trial by the Walter Reed Army Medical Center and the American College of Surgeons (ACOSOG-Z6091) attempted to answer this question, but unfortunately, closed to accrual 1 year after opening in 2011. The primary reason for failure to accrue was patients' perception that randomization to an arm without IPC was unacceptable.

A second French multicenter randomized controlled trial (Prodige 7) recently completed accrual. In this trial, 280 patients with colorectal carcinoma underwent CRS and were randomly selected to receive HIPEC with oxaliplatin over 30 minutes at a minimum of 42°C and preceding intravenous 5-FU/leucovorin bolus or no HIPEC). Data analysis is ongoing. The primary endpoint is 3-year and 5-year overall survival. It is noteworthy that most investigators use mitomycin C as the HIPEC regimen and not oxaliplatin. Thus, the results of this trial might not change their clinical practice. Nevertheless, the results, which are expected to be reported this spring, are eagerly awaited.

MORBIDITY AND MORTALITY

The morbidity and mortality of CRS plus IPC are substantially higher than those of either systemic chemotherapy or CRS alone and should be addressed. In retrospective reviews, the range of postoperative mortality has been reported to range from 0% to 12%.[18] In the two largest studies, including the Dutch randomized study, the range was 3% to 8%.[15,17] Grades 3 and 4 toxicities have been reported in between 23% to 55.6% of patients, including respiratory complications, septic shock, and pulmonary embolism. Hematologic toxicity including hemorrhage, fistulae, peritonitis, cerebral stroke, and renal insufficiency were the most common complications.[15,17,18] In addition, there is a steep learning curve associated with performing CRS/HIPEC, requiring approximately 140 procedures to develop expertise.[20] Similarly, a more recent study found that approximately 180 and 90 CRS/HIPEC procedures

are required to improve operative and oncologic outcomes, respectively.[21] These data exemplify the importance of developing well-organized, multidisciplinary teams that consists of surgeons, perfusionists, anesthesiologists, intensivists, nutritionists, oncologists, and nurse specialists to work together in lowering the associated morbidity and mortality of CRS/HIPEC procedures.

Stringent patient selection is also critical to optimizing operative and oncologic outcomes of patients undergoing CRS/HIPEC. Patients older than 70 and those with significant comorbidities have higher rates of perioperative morbidity and mortality after CRS/HIPEC.[22] To avoid treatment-related morbidity and mortality associated with CRS/HIPEC, high-risk patients may be offered alternative treatments such as systemic therapy alone or CRS alone, particularly in the absence of prospective data that demonstrates the superiority of CRS/HIPEC. The timing of surgery also affects patient outcomes. To coordinate the timing of CRS/HIPEC, patients with metastatic disease confined to the peritoneal cavity should be seen by both the experienced CRS/HIPEC surgeon and the medical oncologist at the time of diagnosis of carcinomatosis or isolated peritoneal disease recurrence. Considerations that influence the timing of CRS/HIPEC include response to systemic chemotherapy, availability of chemotherapy options, and the emergence of treatment-related toxicities. Treatment with effective systemic chemotherapy prior to CRS/HIPEC provides the advantage of reducing the bulk of disease identified at surgery, and, thereby, potentially lowering the initial PCI at the time of CRS/HIPEC.

CONCLUSIONS AND FUTURE DIRECTIONS

Although the data are difficult to interpret because of the lack of large randomized studies and the presence of numerous institutional series, CRS and IPC may provide a benefit to a certain subset of patients with peritoneal carcinomatosis of colorectal origin. The data available do demonstrate that the extent of peritoneal disease greatly affects outcomes. It is conceivable that patients with limited peritoneal disease that can be completely resected (CCR0) may experience a cure, but it is more likely that they will at least achieve better control of disease. The question remains whether the benefit is derived from CRS alone or the addition of IPC. Moreover, if IPC is helpful, it remains debatable whether HIPEC or EPIC is the best route. The French Prodige study will hopefully provide insight into the benefit of adding IPC to CRS. An ongoing study at Memorial Sloan Kettering Cancer Center is evaluating CRS plus HIPEC compared with EPIC in patients with peritoneal carcinomatosis of colorectal or appendiceal origin. As is the case with most therapies, molecular and genetic profiling may identify patients who would benefit from regional therapies. Until these predictive profiles are identified, the optimal approach for patients with peritoneal carcinomatosis will remain controversial.

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GASTROINTESTINAL (NONCOLORECTAL) CANCER

Hepatocellular Carcinoma Tumor Board: Making Sense of the Technologies

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Hepatocellular Carcinoma Tumor Board: Making Sense of the Technologies

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OVERVIEW

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death, with a rising global incidence. The vast majority of HCC cases occur in the setting of liver cirrhosis, mainly due to chronic hepatitis C (HCV) or hepatitis B (HBV) viral infections, alcohol consumption, and nonalcoholic fatty liver disease. The new approval of curative therapy with two NS5A inhibitors, ledipasvir and sofosbuvir, for the treatment of HCV will no doubt affect HCC incidence and outcome. No studies have evaluated the use of the new antivirals in patients with HCC. Staging and scoring remain an integral part of the management of patients with advanced HCC. Curative therapies for the treatment of HCC are evolving. Improvements in surgical techniques and risk stratification for orthotopic liver transplantation (OLT) have expanded access and improved the outlook for patients suffering from HCC. Interventional locoregional treatments continue to play a key role in the management of HCC. Transarterial chemoembolization is considered the standard of care for patients with noninvasive multinodular tumors at the intermediate stage. Bland embolization appears to have similar virtues in some studies. Y90 radioembolization represents a promising treatment option for patients unfit or refractory to transarterial chemoembolization. The advent of sorafenib as a standard of care with an improvement in survival sadly remain the only major breakthrough in the treatment of advanced HCC, with mounting negative data from multiple clinical trials. Advances in immunotherapy and customized therapy may hopefully help reverse this tide.

Hepatocellular carcinoma is a leading cause of cancer-related death, with a rising global incidence.[1] The vast majority of HCC cases occur in the setting of liver cirrhosis, usually because of chronic HCV or HBV, alcohol consumption, nonalcoholic fatty liver disease, among others. Because the majority of patients with HCC have cirrhosis, it is important to understand it and its complications, while we focus on the recent advancements in prevention of cirrhosis-causing etiologies, specifically HCV. This manuscript also addresses the recent developments in the curative and palliative whole treatment armamentarium for HCC from surgery and transplant through local therapies, up to systemic treatment including targeted and immunotherapies.

CIRRHOSIS AND LIVER DYSFUNCTION

Cirrhosis is the outcome of a relentless inflammatory event that ultimately leads to hepatic fibrosis in response to a chronic liver disease (e.g., HCV), to the point where most of the liver parenchyma is replaced by scar. This starts a steady hepatic decompensation phenomenon, along with a risk of developing HCC. Hepatic decompensation includes the development of jaundice, ascites, variceal hemorrhage, hepatic encephalopathy, hepatopulmonary syndrome, or portopul-

monary hypertension. Cirrhosis can be compensated or decompensated, with a 2-year survival of 90% compared with 54%, respectively.[2] HCC is the other important complication of cirrhosis and occurs at an annual incidence rate of 2% to 3%.[3] The presence of cirrhosis and its complications will affect the prognosis and management of patients with HCC. Multidisciplinary management including hepatology is critical in the care for patients with advanced HCC.

The Child-Turcotte classification system was developed in 1964 to risk-stratify patients undergoing shunt surgery for portal decompression at the University of Michigan. In 1972, Pugh modified the Child-Turcotte system, and it became known as the Child-Turcotte-Pugh score, also known for short as the Child-Pugh score. The Child-Pugh score is composed of levels of albumin, prothrombin time, and total bilirubin and also with the presence or absence of clinical hepatic encephalopathy and ascites. Based on these variables, points are assigned and patients are classified as A, B, or C. Although empirically derived, the Child-Pugh has been shown to accurately predict outcomes in patients with cirrhosis and portal hypertension, and it continues to be used today. Because it is simple and does not require complicated calculation, this tool is widely used by clinicians to assess the risk of mortality in patients with cirrhosis. Another important system to as-

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sess liver function is the Model for End-Stage Liver Disease (MELD)— composed of serum total bilirubin, serum creatinine, and international normalized ratio—and it has been shown to be better at predicting mortality in patients with cirrhosis when compared to the Child-Pugh score.[4] This combined with its purely measurable parameters made the MELD score instrumental in helping to allocate donated livers for transplant based on the immediate need of the receiving patient. The Child-Pugh continues to be a reference scoring system for the assessment of liver function, and it is included in many HCC clinical trials as a reference. There have been an endless number of prognostic scoring systems for HCC with a continued debate over their validity.[5] However, a measure of hepatic function is important in the assessment of patients with HCC.

ADVANCEMENTS IN THE TREATMENT OF HEPATITIS C

HCV still lacks a preventative vaccine like that of HBV, which has helped decrease the incidence of HCC in high-risk countries. However, recent developments in direct-acting antiviral agents for HCV infection have shown potential to alter the natural history of the infection and, ultimately, affect the incidence of HCC.

Certain antiviral agents act directly on HCV targets, whereas others target host proteins that are vital for the replication of HCV. Among the viral targets are the NS3/4A serine protease, which cleaves the HCV polyprotein, and the NS5B RNA-dependent RNA polymerase. However, another target, the nonstructural protein 5A (NS5A), has claimed success as a therapeutic target for HCV because of its importance in the assembly of the cytoplasmic membrane-bound replication complex and the high potency of its inhibitors both clinically and preclinically.[6]

The US Food and Drug Administration (FDA) approved the combination of two NS5A inhibitors, ledipasvir and sofosbuvir, a fixed, single pill combination for the treatment of HCV.[7] A 12-week course of treatment has shown a sustained virologic response of 90% for genotype 1. When patients with compensated cirrhosis were treated for 12 weeks, there had a sustained response rate of 96%.[8] The ledipasvir and sofosbuvir combination appears to be very well tolerated, with fatigue and headaches as the most common side effects. Another new agent recently approved by the FDA for the treatment of HCV is a pack containing a combination of a protease inhibitor ABT-450 (ritonavir, ABT-450/r), an NS5A inhibitor (ombitasvir), and a nonnucleoside polymerase inhibitor (dasabuvir) plus ribavirin.[9] A 12-week course showed a sustained virologic response of 96.2% (95% CI, 94.5 to 97.9) in genotype 1 infection. The pack was used in compensated cirrhosis, and 12 weeks of treatment led to a sustained virologic response of 92%.[10] This treatment has shown to be well tolerated, with fatigue, nausea, pruritus, and insomnia as the most common reactions.

With the advent of new curative anti-HCV therapy, it is still unclear how this will affect HCC incidence and outcome. No studies have evaluated the use of the new antivirals in patients with HCC.

CURATIVE THERAPIES

Curative therapies for the treatment of HCC are evolving. Improvements in surgical techniques and risk stratification for orthotopic liver transplantation (OLT) have expanded access and improved the outlook for patients suffering from HCC.

Liver Transplantation

HCC was one of the earliest recognized indications for OLT and remains a leading indication for OLT in adults and children today.[11] The proposal of the Milan Criteria by Mazzaferro et al in 1996 was a sentinel event within the transplant community as it was the first successful attempt to stratify disease burden at OLT with post-OLT outcomes.[12] The limits of the Milan criteria are a single lesion of 5 cm or less in diameter or no more than three lesions, none of which are more than 3 cm in diameter. When the Milan criteria are fulfilled, the post-OLT survival of recipients transplanted because of HCC was not significantly different than OLT recipients, with no diagnosis of HCC. This observation led to the subsequent stratification of OLT candidates into those within or outside Milan criteria. The distinction is significant, as candidates within Milan criteria receive prioritization for OLT and are eligible for automatic progression toward OLT that is not dependent on a decline in their physiology.[13] All other wait list candidates progress toward OLT based on their risk of isolated liver failure as determined by their individual MELD scores.

KEY POINTS

- Hepatocellular carcinoma (HCC) continues to have a rising global incidence.
- A 12-week course of treatement with NS5A inhibitors ledipasvir and sofosbuvir has shown a sustained virologic response up to 96% for patients with hepatitis C viral infection genotype 1.
- The Metro Ticket algorithm asserts that the further one deviates from the Milan criteria with respect to tumor burden in applying liver transplant, the higher the "price" one pays with long-term disease recurrence.
- Despite the theoretical potential synergies between locoregional and systemic therapies with antiangiogenic properties such as sorafenib all clinical trials completed so far have failed to provide evidence of a clinical benefit in that setting.
- Sorafenib remains the sole standard of care for advanced HCC with an improvement in survival to 10.7 months compared to 7.9 months for placebo (0.69; 95% CI, 0.55 to 0.87).

When considering OLT for HCC, transplantation is not restricted to patients within Milan criteria. Indeed, there are no limits to the tumor burden that can be addressed by OLT. The only requirements are identification of a recipient, availability of a donor allograft, and a stable mechanism to pay for services and post-OLT immunosuppressive medications. Two groups widely recognized as performing well after OLT who do not meet Milan criteria are patients without cirrhosis with a larger tumor burden and patients who are subsequently downstaged to within Milan criteria by locoregional therapy.[14] Few long-term data exist on the outcomes of down-staging; however, at the present time, down-staging HCC to within Milan criteria is recognized within the transplant community as an indication to resume automatic prioritization toward OLT.

Other institutions, including the University of Chicago, have specific programs to address OLT for patients with cirrhosis with disease burden exceeding the Milan criteria. These programs typically employ aggressive locoregional therapy to obtain local control, with a period of watchful waiting to exclude extra-hepatic disease. Locoregional therapy typically includes transarterial chemoembolization (TACE) or yttrium-90 (Y90) microsphere embolization in conjunction with percutaneous or laparoscopic radio frequency ablation (RFA). Patients who tolerate therapy and demonstrate no evidence disease progression qualify for OLT utilizing extended-criteria donor allografts. Multiple centers have reported excellent long-term survival based on the Metro Ticket algorithm for management of HCC.[15]

The Metro Ticket algorithm, initially proposed by Mazzaferro, simply asserts that the further one deviates from the Milan criteria with respect to tumor burden in applying OLT for HCC, the higher the "price" one pays with long-term disease recurrence.[16] Several groups have proposed alternative classification strategies for HCC. The most notable is the University of California San Francisco criteria that represents a modest expansion of the Milan criteria but lacks long-term follow-up data.[17]

Additional information outside the total number of lesions and their maximal diameter that are valuable in assessing the applicability of OLT to HCC include alpha-fetoprotein, tumor differentiation, and evidence of vascular invasion. Alpha-fetoprotein levels in excess of 1,000 ng/mL at presentation are a poor prognostic indicator for maturation to OLT and should trigger triage to a high-risk protocol.[18] Although not formally a component of an OLT evaluation for HCC, histology consistent with poorly differentiated HCC is also a negative prognostic indicator for maturation to OLT. Our practice does not mandate histology during the evaluation process but to routinely obtain histology at the time of RFA therapy if indicated. Similarly, the observance of vascular invasion, either macroscopically as venous thrombosis/invasion or microscopically on histology, should direct the patient to a high-risk protocol.[18,19]

The UCSF group reported a large series of long-term outcomes among patients who underwent downstaging for potential liver transplantation compared with patients within Milan criteria. Patients outside Milan were categorized as a large single mass (5 cm < diameter ≤ 8 cm), 2 or 3 lesions (3 cm < one mass ≤ 5 cm with total tumor diameter ≤ 8 cm), and > 3 lesions (each ≤3 cm with total tumor volume ≤ 8 cm). Overall results were excellent, with over half of the downstaging group maturing to liver transplantation. The 1- and 2-year cumulative probabilities for dropout were 24.1% and 34.2% in the down-staging group versus 20.3% and 25.6% in the within Milan group (p = 0.04); however, Kaplan-Meier 5-year post-transplant survival and recurrence-free probabilities were not significantly different. In the multivariate analysis, only pretreatment alpha-fetoprotein ≥ 1,000 ng/mL, Child's class cirrhosis significantly predicted dropout.[15,19,20]

Surgical Resection

Surgical resection remains the standard of care for the treatment of HCC. Traditionally, surgical resectability has been a function of disease burden as well as estimation of functional hepatic reserve as determined by the Child-Pugh score. New surgical techniques combined with improved understanding of disease progression in patients with cirrhosis are now challenging this traditional rationale. The surgical technique of associating liver partition with portal vein ligation for staged hepatectomy as advocated by Schadde and others offers the potential to expand surgical resection to a larger tumor burden within the liver.[22] Their data demonstrate that this technique may allow a larger amount of multifocal disease within the liver to be surgically approached and may enhance regeneration. Promising early data suggest efficacy among patients with cirrhosis who are not candidates for OLT. The current donor shortage and the psychosocial/medical/insurance restrictions placed upon candidacy for liver transplantation precludes this from ever displacing surgical resection as the standard of care.

Salvage Transplantation

Improved understanding of the limitations of salvage transplantation has significantly advanced triage of patients between surgical resection and OLT. Salvage transplantation is the practice of OLT following curative surgical resection. Early data supporting the practice of salvage transplantation re-enforced the traditional mantra of exhausting all surgical options before progressing to OLT. However, recent data examining the role of salvage transplantation stratified by indication for cirrhosis is challenging conventional wisdom. When the indication for cirrhosis has been removed from the patient's physiology, as in abstinence from alcohol or eradication of a viral hepatitis, the benefits of salvage transplantation are preserved. However, attempting salvage transplantation in the setting of patients who have ongoing liver injury, as in hemachromatosis, primary biliary cirrhosis, or an untreated viral hepatitis, has very low efficacy. Therefore, a thorough understanding of the patient's underlying liver disease and recognition of continuing liver injury are essential to appropriate selection of therapy. Patients without con-

tinuing liver injury should be triaged to maximally aggressive surgical resection with salvage transplantation reserved for therapeutic failures. Conversely, surgical resection has very little efficacy in all but the most minimal disease burden in the presence of continuing liver injury. As these patients have a low probability of maturing to salvage transplantation, they will benefit from early referral for OLT.[23]

Ablation

Ablation techniques have evolved considerably over the past 20 years and are increasingly used to definitively treat small HCC tumors. Several methods for focal tumor destruction have been developed and clinically tested. Although RFA has been the most popular technique to date, several alternate technologies—including thermal and nonthermal methods— have recently been adopted, as they seem to overcome some of the specific limitations of RFA.[24]

Several studies have reported long-term outcomes of RFA in patients with small, unresectable tumors and Child-Pugh class A liver disease, and they demonstrate 5-year survival rates as high as 50% to 70%.[25] The question remains whether RFA can compete with surgical resection as a first-line treatment for HCC. Randomized clinical trials of RFA and surgery reported to date have failed to provide an unequivocal answer to this question.

Recurrence after surgery or ablation remains a serious concern. A randomized phase III study comparing adjuvant sorafenib to placebo after curative resection or ablation showed no difference in recurrence-free survival (33.4 for sorafenib versus 33.8 months for placebo, hazard ratio [HR] 0.940; 95% CI, 0.780 to 1.134; p = 0.26).[26]

Although 18F-FDG PET-CT is not part of current routine diagnostic work-up for patients with HCC, studies have suggested that uptake of 18F-FDG is associated with poor tumor differentiation and may be a predictor of recurrence and worse outcomes following surgical or locoregional treatment.[27,28] These results will need to be validated in larger prospective cohorts.

PALLIATIVE LOCAL THERAPIES

Interventional locoregional treatments play a key role in the management of HCC. TACE is considered the standard of care for patients with noninvasive multinodular tumors at the intermediate stage. Bland embolization appears to have similar virtues in some studies. Y90 radioembolization represents a promising treatment option for patients unfit or refractory to TACE.

Transarterial Treatments

TACE is the most widely used treatment for patients with HCC unsuitable for radical therapies worldwide.[29] The most important advance in TACE therapy has been the drug-eluting beads for transarterial administration, which have been shown to reduce liver toxicity and systemic drug exposure compared to standard TACE.[30]

Conventional TACE regimens are based on the administration of an anticancer-in-oil emulsion followed by embolic agents. The key component of this procedure is lipiodol, which is used both as a vehicle to carry and localize the chemotherapeutic agent inside the tumor and as an embolic agent for tiny tumor vessels. Randomized, controlled trials and meta-analyses have shown that TACE improves survival with respect to best supportive care, extending the median survival from 16 to 19–20 months.

However, such trials were performed more than a decade ago. Distinct technical advances in the performance of TACE and improved patient selection and management have taken place since the completion of these studies.[31] In a randomized phase II study comparing TACE using LC Bead loaded with 150 mg of doxorubicin to bland transarterial embolization (TAE) with Bead Block microspheres, there was no difference in median progression-free survival (6.2 vs. 2.8 months; p = 0.11) or overall survival (19.6 versus 20.8 months; p = 0.40) for Bead Block and LC Bead, respectively.[32] Given a comparable safety profile, and similar outcomes, the advancement in technology and super selectivity in arterial blockade place the role of added doxorubicin into question.

An unsettled issue in the management of patients treated with embolization is the assessment of tumor response and the criteria for treatment discontinuation. Several recent investigations conducted in the United States, Europe, and Asia have shown that the assessment of tumor response by modified Response Evaluation Criteria in Solid Tumors predicts overall survival in patients with HCC treated with TACE.[33] It has been suggested that TACE should be discontinued in patients in whom an objective response in the treated tumor has not been achieved after two treatment cycles.[34]

Radioembolization

Radioembolization is a form of intra-arterial radiation therapy that was developed to capitalize on the arterial perfusion of HCC, with the aim of delivering radiation tumoricidal doses to liver tumors.[35] Radioembolization with Y90 is challenging the current paradigm of HCC treatment. Multiple centers around the world have provided compelling data that suggest a clinical role in patients with portal vein thrombosis as well as in downstaging to transplantation or conversion of patients with surgically inoperable disease (because of small liver remnant) to potential cure with resection. This approach, however, still lacks randomized, controlled study data.

Combination of Locoregional and Systemic Therapies

The key downside to locoregional treatment is the high rate of tumor recurrence, which exceeds 70% at 5 years after local ablation of early-stage HCC.[36] Several experimental studies have suggested potential synergies between locoregional and systemic therapies with antiangiogenic properties, such as sorafenib. Unfortunately, the clinical trials completed so far failed to provide evidence of a clinical benefit. Such an ap-

proach failed to provide a clinically meaningful improvement in time-to-progression (TTP) compared with drug-eluting bead TACE alone in the randomized phase II SPACE study.[37] Median TTP was 169 days in the sorafenib group and 166 days in the placebo group, (HR 0.797; 95% CI, 0.588 to 1.080; p = 0.072). The phase III trial that compared the efficacy and safety of brivanib with placebo as adjuvant therapy to TACE in patients with unresectable HCC has similarly disappointing results: the median overall survival was 26.4 compared with 26.1 month, respectively (HR 0.90; 95% CI, 0.66 to 1.23; log-rank p = 0.5280).[38]

The combination of locoregional and systemic therapy has so far been investigated mostly in patients with limited tumor burden, for whom antiangiogenic treatment was administered on top of the standard locoregional approach. Another developing idea views systemic and interventional therapies as complimentary modalities, which allows patients with advanced-stage disease to be candidates for locoregional treatments.[39]

SYSTEMIC THERAPY

The advent of sorafenib as a standard of care with an improvement in survival to 10.7 months compared to 7.9 months for placebo (0.69; 95% CI, 0.55 to 0.87; p < 0.001)[40] was a major breakthrough in the treatment of advanced HCC, after decades of disappointing attempts to identify a standard of care therapeutic agent.[41] The past 8 years, however, have been disappointing with mounting negative data from multiple clinical trials. Few studies with promising early robust results may turn the tide around.

First-Line Therapy

A phase II study compared doxorubicin plus sorafenib to doxorubicin plus placebo in 96 patients with advanced HCC and Child-Pugh A.[42] The primary endpoint, median TTP, was 9 months for the doxorubicin and sorafenib arm compared with 5 months for the doxorubicin and placebo arm. An exploratory comparison of overall survival between the two arms showed a significant difference of 13.7 months in favor of doxorubicin and sorafenib compared with 6.5 months for doxorubicin and placebo (p = 0.0049, HR 0.45). A potential synergistic effect between doxorubicin and sorafenib that is based on the dissolve of an inhibitory dimer of ASk-1 and Raf, plus other putative mechanisms, may explain the improved outcome.[43] A large randomized phase III trial comparing the combination of sorafenib and doxorubicin with sorafenib alone in the first-line setting[44] and a phase II study of this regimen in the second-line setting after sorafenib failure[45] are currently underway.

Second-Line Therapy

Several studies evaluating novel therapeutics in the second-line setting have been met with disappointment. These include brivanib[46] and otherwise known active therapies such as everolimus[47] and ramucirumab.[48] The perception of low-hanging fruit when comparing to a placebo in the second-line setting is a reminder of the continued advancement in the total care of patients with HCC who generally are living longer than previously perceived.

The biosynthesis of the nonessential amino acid arginine occurs as part of the urea cycle and is dependent on the enzymes argininosuccinate synthetase and argininosuccinate lyase. Messenger RNA encoding argininosuccinate synthetase is not present in subsets of HCCs; therefore, arginine must be extracted from the circulation. Pegylated arginine deiminase (ADI-PEG 20) is an arginine-degrading enzyme isolated from *Mycoplasma* that is formulated with polyethylene glycol (molecular weight 20 kd). Based on encouraging phase II data,[49] ADI-PEG20 is currently being evaluated in a phase III trial in comparison to placebo with patients with advanced HCC in the second-line setting.[50]

Overexpression of c-MET and its ligand HGF occur in up to 80% of human HCC tumors.[51] Tivantinib, a selective MET receptor tyrosine kinase inhibitor, was evaluated at two doses in a randomized, placebo-controlled phase II trial for patients with advanced HCC in the second-line setting. It was found that patients with high MET-expressing tumors, tivantinib therapy resulted in a median overall survival of 7.2 months compared with 3.8 months for placebo (HR 0.38; 95% CI, 0.18 to 0.81). Considering that high tumoral MET expression was associated with an improved overall survival when compared with low tumoral MET expression (3.8 months versus 9 months, HR 2.94; 95% CI, 1.16 to 7.43), a randomized phase III study of patients with advanced HCC and high MET-expressing tumors only in the second-line setting followed and is currently underway.[52] Cabozantinib, an inhibitor of MET and vascular endothelial growth factor receptor 2, has also shown promising efficacy data in a cohort of 41 patients with advanced HCC.[53] Median progression-free survival for the cohort was estimated at 4.2 months. A phase III study cabozantinib is underway.[54] Because tivantinib and cabozantinib are both multitargeted tyrosine kinases, their antitumor activity is not solely dependent on MET pathway inhibition, and selection for MET overexpressing tumors, such as for tivantinib, may not be warranted when using such class of drug.

Immunotherapy

Immune escapes have been identified to carry a poor outcome with a high likelihood of metastatic spread.[55] Tremelimumab, a monoclonal antibody to cytotoxic T-lymphocyte antigen-4, has demonstrated antitumor activity in patients with heavy pretreated unresectable and metastatic hepatitis C–related HCC.[56] Partial response rate was 17.6% and TTP was 6.48 months (95% CI, 3.95 to 9.14). Similarly data have suggested that program death receptor-1 and program death receptor-1 ligand (PDL-1) can suppress HCC,[57] and several studies are investigating these agents in HCC as monotherapy.[58,59] Preliminary data from a multiarm expansion study of MEDI4736, an anti-PDL-1 antibody in patients with advanced solid tu-

mors including HCC, has shown promise.[60] An expansion study of MEDI4736 was initiated in multiple cancer types including HCC. The study continues to enroll patients and generate more mature follow-up data.

CUSTOMIZED THERAPY

Recent work by many groups has attempted to recognize the key drivers and potential targets for advanced HCC.[61,62] No clear patterns have evolved so far, short of recognizing certain genetic variation in select cohort of patients. A more global approach that attempts to evaluate cohorts of patients with HCC with specific ethnicity and etiology and that correlates genetic findings with clinical outcomes may make headway toward custom-made therapy for patients with advanced HCC. One of such current global efforts led by Memorial Sloan Kettering Cancer Center is also attempting to interrogate the genetic profile of each patient into specific clusters that are yet to be discovered.

Disclosures of Potential Conflicts of Interest

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Making Sense of Emerging Therapies in Pancreatic Cancer: Are We Finally on the Right Track?

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Making Sense of Current and Emerging Therapies in Pancreatic Cancer: Balancing Benefit and Value

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OVERVIEW

Pancreatic cancer remains the fourth leading cause of cancer deaths in the United States with a dismal prognosis and a 5-year survival of less than 5% across all stages.[1] In 2014, there were approximately 46,420 new cases of pancreatic cancer with only 9% of patients having localized disease.[2] Given that the vast majority of patients present with advanced disease, much of the focus for drug development has been in the metastatic setting, which is evident with the advent of two combination chemotherapy regimens for this indication. Although conventional cytotoxic chemotherapy remains the standard of care, an ongoing search for novel therapeutic approaches continues. We will highlight several new approaches here, with a particular emphasis on immunotherapeutic strategies. We will also introduce concepts regarding the potential economic effects associated with the development and implementation of new treatments in pancreatic cancer.

Conventional cytotoxic chemotherapy remains the standard of care for pancreatic cancer. Table 1 highlights major findings from key clinical trials in advanced pancreatic cancer. Before recent advances, the last significant therapy approved for pancreatic cancer was erlotinib in 2007, based on a phase III randomized control trial showing that this agent when added to gemcitabine improved survival.[3] However, because the degree of survival improvement was of questionable clinical significance and at the expense of significant toxicities (62% grade 3 to 4 adverse events), the combination has never found significant traction in the treatment of pancreatic cancer. During the past several years, two chemotherapy regimens, FOLFIRINOX and gemcitabine/nab-paclitaxel, have emerged as new standards of care for the first-line treatment of metastatic pancreatic cancer, both based on randomized phase III trials that show more clinically meaningful benefits when compared with gemcitabine.

Despite these recent advances, the median survival for patients with metastatic disease remains less than a year, highlighting a desperate need to continue the developmental therapeutic path in pancreatic cancer.

RECENT DEVELOPMENTS WITH TARGETED THERAPEUTIC AGENTS

Beyond conventional cytotoxic chemotherapy, the modern trend in developing novel therapeutic approaches offers promise for improving the outlook of patients with advanced pancreatic cancer.

TARGETING TUMOR MICROENVIRONMENT

The stromal compartment in pancreatic cancer is dense and contributes to the aggressive nature of this tumor by fostering tumor growth and enhancing drug resistance by inhibiting effective penetration of chemotherapy. With an increased understanding of the importance of the role of the tumor microenvironment and its role in tumor proliferation, agents aimed at targeting the tumor microenvironment is an area of increased interest in pancreatic cancer.[4-9] However, previous attempts to target the tumor microenvironment, in particular with Hedgehog signaling inhibitors, have proved unsuccessful.[10,11]

Recent early phase studies have shown promising results in targeting tumor stroma in pancreatic cancer with PEGPH20. PEGPH20, a pegylated form of recombinant hyaluronidase, has been shown to successfully degraded hyaluronic acid (HA), a primary component of tumor peristroma, leading to the re-expansion of tumor microvasculature and improving the delivery of gemcitabine.[12] Early studies of PEGPH20 in combination with gemcitabine have demonstrated provocative progression-free survival and overall survival (OS) in patients with elevated levels of hyaluronic acid,[13] which has resulted in two ongoing randomized phase II trials in meta-

TABLE 1. Standard Chemotherapy Regimens in Metastatic Adenocarcinoma of the Pancreas

Chemotherapy Regimen	Sample Size	Survival, Median (Months)	Hazard Ratio	Objective Response Rate	Toxicities (Grade 3 to 4)	Author
Gemcitabine vs. 5-FU	126	5.65 vs. 4.41	Not reported	5.4	Neutropenia 25.9%	Buris III et al 1997[44]
Gemcitabine/erlotinib vs. gemcitabine	569	6.24 vs. 5.9	0.82	8.6	62% (fatigue 15%, infection 17%)	Moore et al 2007[3]
FOLFIRINOX vs. gemcitabine	342	11.1 vs. 6.8	0.57	31.6	Fatigue 23.6% neutropenia 45.7%	Conroy et al 2011[45]
Gemcitabine/nab-paclitaxel vs. gemcitabine	861	8.5 vs. 6.7	0.72	23	Fatigue 17% neutropenia 38%	Von Hoff et al 2013[46]
5-FU/leucovorin + MM-398 vs. 5-FU	417	6.1 vs. 4.2	0.57	16	Fatigue 14% neutropenia 20% diarrhea 13% vomiting 11%	Von Hoff et al 2014[47]

static pancreatic cancer (ClinicalTrials.gov NCT01959139 and NCT01839487).

TARGETING THE RAS PATHWAY

Targeting signaling pathways in cancer remains an attractive therapy in pancreatic cancer. Given the nearly universal presence of activating *KRAS* mutations in pancreatic cancer and its key function in cell survival and proliferation, *KRAS* represents an ideal target; although, its relevance as a therapeutic target is not fully established.[14-16] Targeting *RAS* directly is a challenge; one approach using oncolytic viruses is described below. Attempts have been made to inhibit downstream effector molecules to *RAS,* although cross-talk between parallel downstream signaling pathways and negative loop feedback inhibition have been indicated as potential mechanisms for resistance and highlight the need to inhibit multiple pathways simultaneously.[17]

TAKING ADVANTAGE OF SYNTHETIC LETHALITY

For a distinct group of patients with pancreatic cancer, the concept of synthetic lethality may afford a specific treatment strategy. Synthetic lethality occurs when a combination of mutations in two or more genes leads to cell death, whereas, a single mutation does not and by itself remains viable. Tumors harboring defective DNA repair mechanisms render them vulnerable to synthetic-lethality approaches, leading to the use of targeted agents that induced the death of tumor cells while sparing normal cells. Mutations in genes, including tumor suppressor genes (*BRCA 1/2, ATM*), may confer an increased sensitivity to DNA-damaging cytotoxic chemotherapy including platinum analogs and PARP inhibitors because of the associated defective homologous recombination and an inability to mount efficient DNA repair.[18,19] In specific subgroups of patients, including those of Ashkenazi Jewish descent and individuals with a family history of pancreatic cancer, the prevalence of germ-line mutations of *BRCA1* and *BRCA2* has been reported in as many as 19%.[20,21] For patients with germ-line *BRCA1/BRCA2* mutations, a phase III randomized, double-blind study, the POLO trial, is investigating the use of the PARP inhibitor olaparib in patients with metastatic pancreatic cancer whose disease has not progressed on first-line platinum-based chemotherapy (ClinicalTrials.gov NCT02184195).

KEY POINTS

- Pancreatic cancer remains a devastating disease with an increasing prevalence and the highest mortality rate of any malignancy.
- Cytotoxic chemotherapy remains the primary treatment for advanced pancreatic cancer, with several new combination regimens emerging as first-line standards.
- New agents targeting the tumor microenvironment and cancer-signaling pathways are being investigated in pancreatic cancer.
- Although pancreatic cancer has been mostly considered an immunosuppressive malignancy, developments have renewed interest in immunotherapy as a treatment option in this disease.
- Attention to the value of new therapeutics is critical to prioritizing efforts and selecting treatment for individual patients.

IMMUNOTHERAPEUTIC APPROACHES IN PANCREAS CANCER
Targeting PD-1/PD-L1

Except for melanoma, renal cell carcinoma, and prostate cancer, immunotherapy for solid tumors remains experimental. Tumors resist an immune response by inducing tolerance in tumor-specific T cells and by expressing ligands that bind to inhibitory receptors, or immune checkpoints on T cells, which dampen their immune response against tumors. Immunotherapeutic approaches, notably agents targeting negative regulatory molecules on activated T cells, such as cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), and its binding ligand, programmed death ligand 1 (PD-L1), are showing promise in a number of malignancies. Antagonism of these immune checkpoints can augment the nascent antitumor response from the immune system.

Pancreatic cancer has been mostly considered an immunosuppressive malignancy, with pancreatic cancer cells producing cytokines (transforming growth factor-beta) and surface molecules that mediate immunosuppression (FAsL, PDL-1). Moreover, it has been mostly considered a nonimmunogenic malignancy, since tumor-infiltrating effector T lymphocytes do not represent a histopathologic hallmark for this disease. Therapeutic approaches focusing on overcoming T-cell immunologic checkpoints with anti-CTLA-4 and anti-PD1 monoclonal antibodies alone have failed to demonstrate any meaningful activity in pancreatic cancer to date.[22,23] However, studies investigating the combination of checkpoint inhibitors with "immune resensitizing" agents are currently in development in this disease, as described below.

VACCINE THERAPIES

With molecular identification of human tumor antigens, antitumor vaccine therapies specifically sensitize immune cells against tumor antigens. Several types of vaccinations are under investigation against pancreatic cancer, including whole-cell, peptide, DNA, and vaccines with microorganisms.

GVAX

GVAX is an irradiated whole-cell modified vaccine composed of two irradiated pancreatic cancer cell lines (PANC 6.03 and PANC 10.05) engineered to express granulocyte-macrophage colony-stimulating factor (GM-CSF), a growth factor that plays a key role in stimulating the immune system response by inducing dendritic cell differentiation. Administration of GVAX in addition to standard 5-FU-based chemoradiation as part of adjuvant therapy after pancreatic cancer resection demonstrated promising results in a single-institution phase II trial.[24] Moreover, several studies investigating the immunologic effects of GVAX have demonstrated its ability to create an inflammatory reaction causing an upregulation of PD-L1, suggesting the potential utility of combining this vaccine with immune checkpoint inhibitors.[25,26]

CRS-207

An alternative immune-based strategy undergoing clinical investigation in pancreatic cancer is CRS-207, a live-attenuated *Listeria* monocytogenes (LM) vaccine (CRS-207, Aduro Biosciences, Berkeley, CA) genetically modified to express mesothelin, which is often overexpressed in pancreatic cancer. A recent randomized phase II trial in patients with chemotherapy-refractory metastatic pancreatic cancer suggested a significant improvement in overall survival when sequential treatment with GVAX/CRS-207 was administered, as compared with GVAX alone (median OS, 6.1 vs. 3.9 months; hazard ratio

[HR] 0.59, p = 0.02).[27] These findings have led to an ongoing phase IIB randomized control trial comparing CRS-207 alone to CRS-207 in combination with GVAX or to chemotherapy in previously treated metastatic pancreatic cancer (ClinicalTrials.gov NCT02004262). Another phase II study is investigating the use of GVAX in combination with CRS-207 with or without nivolumab, an anti-PD-1 monoclonal antibody, in previously treated metastatic pancreatic cancer (ClinicalTrials.gov NCT02243371).

ALGENPANTUCEL-L

Algenpantucel-L (NewLink Genetics Corporation, Ames, Iowa) is a whole-cell vaccine made of two human pancreatic cancer cell lines (HAPa-1 and HAPa-2) that are genetically modified to express alpha^{1,3}-galactosyl epitopes (alphaGAL), a carbohydrate present in the cells of most mammals except humans, which have developed pre-existing immunity. On injection, algenpantucel-L induces an immune response that parallels the hyperacute rejection that can occur postorgan transplant. An open-label phase II trial of this vaccine in combination with adjuvant chemotherapy and chemoradiation in resected pancreatic cancer demonstrated promising 1-year disease-free survival and OS rates (62% and 86%, respectively).[28] On this basis, a large phase III trial was recently completed in the United States, evaluating standard adjuvant chemotherapy or chemoradiation with or without algenpantucel-L in resected pancreatic cancer (ClinicalTrials.gov NCT01072981).

ONCOLYTIC VIROTHERAPY

Because of their tumor selectivity and ability to cause cancer cell lysis, oncolytic viruses continue to represent an area of considerable interest in cancer treatment. These viruses selectively target tumor cells through engineered mutations that prevent the binding and replication of the virus in normal, healthy cells and attack specific tumor epitopes that lead to cancer cell death.

Reovirus is a family of naturally occurring, ubiquitous nonenveloped human virus whose replication is dependent on cellular activity of *RAS*; specifically, it is cytopathic in transformed cells possessing an activated *RAS* signaling pathway.[29-32] Given the prevalence of *KRAS* mutations in pancreatic cancer, reovirus has represented a promising and attractive candidate as an oncolytic virus in this disease. Bekaii-Saab et al reported the results of a phase II randomized trial in which 73 patients with metastatic pancreatic adenocarcinoma were randomly assigned to receive carboplatin/paclitaxel alone or in combination with Reolysin.[33] Although this agent was well tolerated overall, it failed to show an improvement in outcomes, including in those patients with *KRAS* mutations. Investigation into other oncolytic viruses (adenovirus, parvovirus, pox virus, measles virus) continues in patients with pancreatic cancer.

TABLE 2. Cost of First-Line Standard Chemotherapy Regimens in Metastatic Pancreatic Cancer*[48]

Regimen	Monthly Costs of Drugs	Monthly Cost of Administration	Monthly Cost of Toxicities**	Total Monthly Cost†
Gemcitabine	$188	$143	$1,032[2]	$1,363
Gemcitabine/ nab-paclitaxel	$9,008	$522	$2,692	$12,221
FOLFIRINOX	$763	$531	$5,940	$7,234
Gemcitabine/ erlotinib	$6,831	$143	$1,032[2]	$8,007

*All costs were calculated in U.S. dollars ($). The unit price of each drug was determined from the 2013 average sales price from the Centers for Medicare & Medicaid Services. Fees for administration and toxicities were calculated according to the 2013 physician fee schedule.[49]
**The cost of growth factor is included.
†The cost of growth factor is based on data extrapolated from the gemcitabine arm in the MPACT trial.[46]

THE JAK/STAT PATHWAY

Recent studies have indicated that *JAK2*/signal transducers and activators of transcription 3 (STAT3) signaling pathways are important for the initiation and progression of pancreatic cancer.[34] In addition to its contribution to tumorigenesis, the clinical symptoms associated with pancreatic cancer, including cachexia and weight loss, reflect a chronic inflammatory state likely related in part to the *JAK*/STAT pathway.[35] Based on these findings, ruxolitinib, a *JAK1/JAK2* inhibitor, is currently under investigation in metastatic pancreatic cancer. A randomized phase II study (RECAP trial) compared the addition of ruxolitinib to capecitabine with capecitabine alone in patients after progression on gemcitabine-based therapy.[36] Although no survival difference was observed in the overall study population, a preplanned analysis in the subgroup of patients with elevated levels of C-reactive protein (CRP) revealed a significant survival benefit in favor of the ruxolitinib-containing arm (HR 0.47, p = 0.01). Based on these findings, two phase III trials, JANUS-1 and JANUS-2, investigating the use of capecitabine with or without ruxolitinib in the first and second-line of therapy, respectively, are ongoing for patients with metastatic pancreatic cancer with elevated CRP, a biomarker of an inflammatory state (ClinicalTrials.gov NCT02117479 and NCT02119663).

CHIMERIC ANTIGEN RECEPTOR T CELLS

Last, albeit in its early stages, the role of autologous T cells manufactured to express chimeric antigen receptors, known as CAR T cells, is under active investigation in a variety of tumor types, including pancreatic cancer. These CARs can recognize specific membrane proteins expressed on tumor cells, such as mesothelin in pancreatic cancer.[37] This adoptive cell transfer approach has produced sustained remissions in hematologic malignancies,[38] but its safety and efficacy in solid tumors requires further study.

THE VALUE OF CURRENT AND EMERGING THERAPIES

Concern has been raised regarding the high costs of new innovations in oncology from a variety of perspectives, including society, payer, and patient.[39] From the patient perspective, high out-of-pocket expenses can affect personal finances and treatment adherence (Table 2). Given the increasing number of treatment options available for patients with advanced pancreatic cancer, coupled with the fact that the benefits of each recent advance have been incrementally modest, it is important to systematically compare the benefits and costs (i.e., the value) of each option. This will allow oncologists to help patients optimize treatment decisions, and payers and policymakers to rationally address resource allocations. The American Society of Clinical Oncology has stressed the importance of recognizing financial implications for patients,[40] and is developing a user-friendly framework for the assessment of value.

Pancreatic cancer treatments highlight the importance of not only considering anticancer drug costs in such analyses, but also supportive care and management of complications that may differ substantially between regimens. For example, recent economic analyses have indicated that although the drug costs associated with gemcitabine/nab-paclitaxel are much higher than those with FOLFIRINOX, the costs associated with supportive measures (including hematopoietic growth factors and hospitalization) are greater with FOLFIRINOX.[41,42] Despite the higher costs associated with administration and toxicities with FOLFIRINOX, the monthly cost of gemcitabine/nab-paclitaxel remains higher. Although cost is one important factor in determining treatment, other factors not limited to quality of life and survival benefit should be considered in any treatment decision. As new treatments are developed, including a number of the newer (and likely very costly) agents discussed above, the inclusion of economic analyses in phase III clinical trials, supplemented by analyses of administrative data, will be essential for prioritizing and applying these various treatment approaches in a thoughtful way. This information will be useful both for our individual patients and for society at large.

CONCLUSION AND FUTURE DIRECTIONS

Despite advances in cancer care and research, pancreatic cancer remains very challenging, with standard treatment regimens providing modest gains at a significant cost. A variety of novel therapeutic approaches, including several targeting the immune system in different ways, have produced promising results and spurred further investigation in both early- and later-phase studies. As these innovations continue to be developed, it is important that we set a high bar to ensure that we bring the greatest value to our patients.[43]

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Relationships are considered self-held and compensated unless otherwise noted. Relationships marked "L" indicate leadership positions. Relationships marked "I" are those held by an immediate family member; those marked "B" are held by the author and an immediate family member. Institutional relationships are marked "Inst." Relationships marked "U" are uncompensated.

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GASTROINTESTINAL (NONCOLORECTAL) CANCER

Nutritional Support in Gastrointestinal Malignancies

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Current and Future Care of Patients with the Cancer Anorexia-Cachexia Syndrome

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OVERVIEW

Many important advances have occurred in the field of cancer cachexia over the past decade, including progress in understanding the mechanisms of the cancer anorexia-cachexia syndrome (CACS) and the development of promising pharmacologic and supportive care interventions. However, no approved agents for cancer cachexia currently exist, emphasizing the unmet need for an effective pharmacologic therapy. This article reviews the key elements of CACS assessment in daily practice, the contribution of nutritional impact symptoms (NIS), the evidence for current pharmacologic options, and promising anticachexia agents in perclinical and clinical trials. It also proposes a model for multimodality therapy and highlights issues pertinent to CACS in patients with pancreatic, gastric, and esophageal cancer.

Many important advances have occurred in the field of cancer cachexia over the past decade, including progress in understanding the mechanisms of CACS and the development of promising pharmacologic and supportive care interventions. However, no approved agents for cancer cachexia currently exist, emphasizing the unmet need for an effective pharmacologic therapy. Patients with CACS may have different priorities; for many, preserving lean body mass (LBM) and function may be important, while for others, maintaining appetite to enjoy meals with their family may be the primary goal. Appetite and weight loss are also associated with important clinical outcomes such as decreased survival, fewer completed cycles of chemotherapy, more treatment side effects, and poorer health-related quality of life.[1-3]

CACHEXIA AND UPPER GASTROINTESTINAL CANCERS

A study by DeWys[4] in 1980, of more than 3,000 patients enrolled in Eastern Cooperative Oncology Group chemotherapy trials, identified the high prevalence of weight loss in cancer and its association with decreased survival. The survival of patients with gastric and pancreatic cancer did not correlate with weight loss (even though 85% of these patients experienced weight loss, and one-third lost more than 10%). Possibly, weight loss may have lost its powerful predictive value in these patients because of their very poor prognosis.[5] A subsequent retrospective study found weight loss in pancreatic and gastric cancer at presentation was associated with poorer quality of life and increased chemotherapy toxicity,

even at lower doses.[6] Outpatients with esophageal or pancreatic cancer have the highest nutritional risk scores, and more than 80% experience anorexia and weight loss even when they have a performance status (PS) of 1.[7]

ASSESSMENT OF PATIENTS

A consensus definition of cancer cachexia is important for clinical trial design and for identifying patients with the syndrome in clinical practice. Ideally, patients who are at risk should be identified early to provide the greatest opportunity for effective intervention. A delay could result in uncontrolled symptoms, poorer quality of life, and more rapid entry into the refractory stage of cachexia. A recent study of body composition imaging by CT of 368 patients shows 5% or less of patients gained muscle within 90 days of death, suggesting the anabolic opportunity for intervention probably exists early in the disease trajectory.[8]

Definition

Cancer cachexia is defined as a multifactorial syndrome characterized by ongoing loss of skeletal muscle mass (with or without loss of fat) leading to progressive functional impairment, which cannot be fully reversed by conventional nutritional support.[9] Based on the current definition, detection of cancer cachexia centers on involuntary weight loss of more than 5% over 6 months (or 2% when evidence of sarcopenia is present).[9,10] Recently, attempts have been made to incorporate anorexia severity, PS, and markers of inflammation, such as C-reactive protein, into staging criteria for the identifica-

tion of precachexia, cachexia, and refractory cachexia. A simple, objective, systemic inflammation–based approach using C-reactive protein and albumin has prognostic value independent of tumor stage, PS, and treatment in a variety of advanced tumors, but it has yet to be incorporated into the screening or staging of cancer cachexia.[11,12] More research is required to identify simple patient-reported outcomes or biomarkers that could help classify patients into early and late stages of cachexia.

Assessment Tools

A brief standardized assessment that includes NIS such as nausea, depression, and severe pain should be performed on all oncology patients who are at risk for CACS (Fig. 1). Unfortunately, the American Society of Clinical Oncology's Quality Oncology Practice Initiative does not currently include any specific questions about appetite,[13] and without systematic inquiry, symptoms such as anorexia may not be identified by oncologists, since patients volunteer few symptoms relative to their total symptom experience.[14]

The 10-item Edmonton Symptom Assessment Scale (ESAS) has shown a high prevalence of multiple symptoms in ambulatory patients with cancer, similar to the symptom burden reported in palliative care populations.[15] The ESAS assesses symptom severity, including appetite, but does not include other CACS-relevant symptoms such as constipation, early satiety, or dysgeusia. A more comprehensive evaluation requires an additional assessment measure such as the Patient-Generated Subjective Global Assessment (PG-SGA): an American Dietetic Society–endorsed questionnaire that identifies additional reversible factors contributing to poor oral intake. A recently validated brief version, the a-PG-SGA, can be completed in less than 5 minutes and provides additional diagnostic and prognostic value for patients with cancer.[16] Using these simple tools for symptom and nutritional assessment, along with a history of 5% or more weight loss during the past 6 months would identify many patients with CACS.

KEY POINTS

- The cancer anorexia-cachexia syndrome (CACS) is common in patients with upper gastrointestinal cancers and is associated with decreased survival and poor tolerance to chemotherapy.
- No approved drugs currently exist for CACS, suggesting an unmet need.
- Preliminary studies using multimodality therapy with pharmacologic and nonpharmacologic interventions have demonstrated improved clinical outcomes.
- A brief standardized assessment to identify CACS and the symptoms contributing to decreased caloric intake is necessary.
- Recent phase II trials have shown improved clinical outcomes for a number of single agents.

Role of Body Composition

Because of the high prevalence of obesity in the general population, many patients may have a normal or elevated body mass index even though they report weight loss and experience profound muscle wasting. Body composition assessment by dual-energy x-ray absorptiometry (DEXA) scan[17] or CT scan may identify patients with occult muscle wasting, consistent with sarcopenia. Patients with the combination of sarcopenia and obesity have a worse prognosis[18] and a higher risk of chemotherapy-related adverse effects.[19] The information derived from routine CT images can provide potentially clinically relevant information beyond assessment of tumor size and response.[20]

Several studies using routine CT imaging in patients with pancreatic cancer have demonstrated relationships between body composition, LBM,[16] impaired lung function,[21] and clinical outcomes. For patients entering a palliative care program, sarcopenia in patients who were overweight was an independent adverse prognostic indicator.[22] Another longitudinal study in patients with locally advanced pancreatic cancer showed that baseline obesity and loss of visceral adipose tissue (VAT) were associated with worse survival.[23] In particular, patients with diabetes who have pancreatic cancer experience accelerated VAT loss and reduced survival compared to those patients without diabetes.[24] In patients receiving neoadjuvant chemotherapy for potentially resectable pancreatic cancer, skeletal muscle loss and VAT loss were correlated with disease-free and progression-free survival, respectively.[25] Although quantification of LBM or fat is not yet conducted in daily clinical practice, CT imaging is emerging as a useful measure of body composition[16] and could influence clinical decision making and chemotherapy dosing in future.

Other modalities have been used for body composition analysis, including bioimpedance (BIA),[26] which relies on the different electrical properties of fat and muscle and—although not as accurate as CT imaging or DEXA—is relatively easy to use and nonburdensome for patients. Additional information provided by BIA such as the ratio of resistance and reactance (phase angle) may be useful for prognostication in several tumor types including pancreatic cancer.[27-29]

CURRENT MANAGEMENT

The clinical assessment and management should focus on nutrition (quantity and composition), symptoms contributing to poor oral intake, weight and body composition, and identification of any reversible metabolic abnormalities (Figs. 2 and 3).

Symptom Management

NIS such as nausea, depression, severe pain, dysgeusia, gastroparesis, and constipation can contribute to decreased caloric intake and weight loss in patients with CACS (Fig. 3). In addition, comorbid metabolic abnormalities such as hypogo-

FIGURE 1. CACS Assessment in Daily Practice

Goal of CACS assessment	• Identifying those at risk • Identifying early signs • Monitoring outcomes of interventions
Type of assessment tool	• Numeric scale for symptoms, includes appetite (ESAS) • Additional checklist for nutritional impact factors, e.g. abbreviated PG-SGA
Individual administering assessment	• Patient (self) or caregiver (ESAS), <5 minutes • Staff, e.g. dietitian (aPG-SGA), <5 minutes
Monitor key outcomes	• Weight change Optional: labs, body composition • Appetite • Fatigue, Physical Activity • Quality of life

CACS: Cancer Anorexia Cachexia Syndrome;
ESAS: Edmonton Symptom Assessment Scale;
aPG-SGA: Abridged Patient-Generated Subjective Global Assessment

nadism, thyroid dysfunction, and vitamin B12 and D deficiencies may contribute to fatigue, muscle weakness, and poor appetite. Other causes of weight loss that have a predominant starvation component such as gastrointestinal obstruction should be identified, especially if they are reversible and respond to endoscopic or surgical treatment

(e.g., stent placement or endoscopic dilation for esophageal obstruction).

A retrospective study of 151 patients with solid tumors referred to a specialized cachexia clinic found a median of three NIS and five or more NIS in 15% of patients.[30] Early satiety was the most common symptom, and it improved in many

FIGURE 2. Muscle Wasting in Cancer
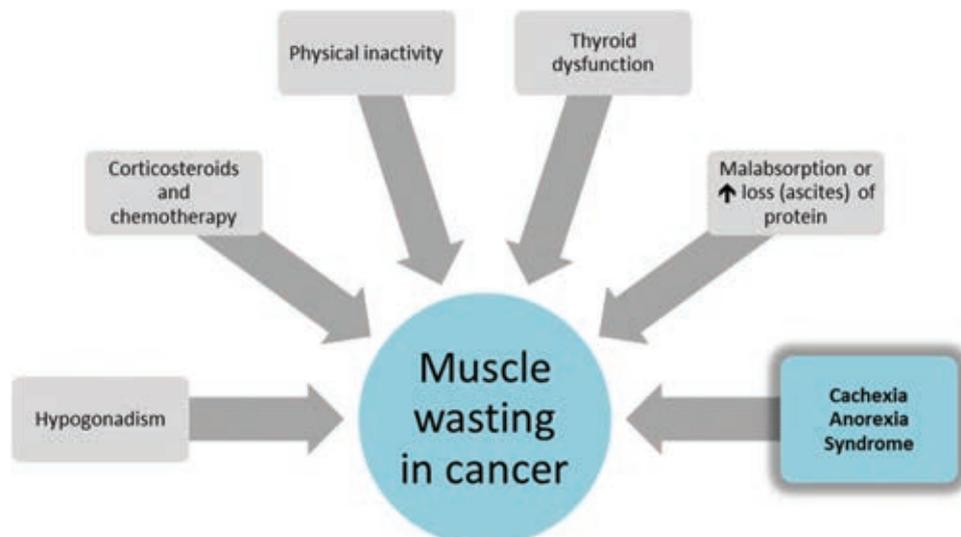
FIGURE 3. Mechanisms of Anorexia in Cancer
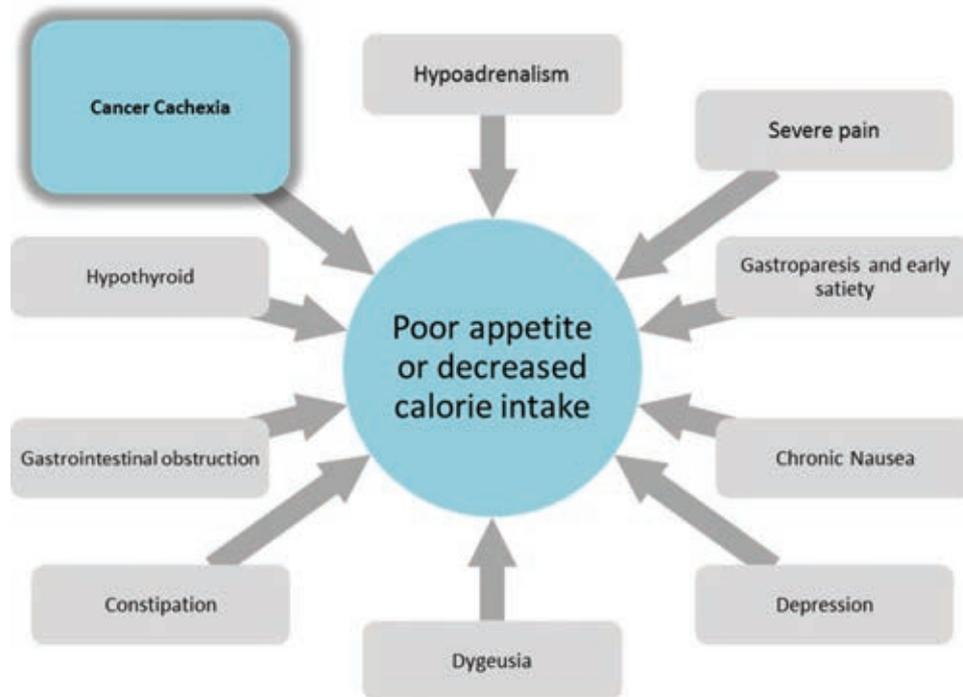
with 10 mg metoclopramide every 4 hours orally. Patients with advanced cancer often have gastroparesis and dysmotility; metoclopramide enables the stomach to accommodate more food and improves motility.[31,32] Although rare, tardive dyskinesia is an irreversible side effect, so the benefits of treatment beyond 3 months should be considered carefully since the duration and total cumulative dose of metoclopramide increase the risk of tardive dyskinesia.

Other NIS can also be effectively managed with readily available inexpensive medications. Constipation, often exacerbated by medications such as opioids and ondansetron may contribute to early satiety and can be effectively managed with laxatives, although few published trials compare bowel regimens.[33] Depressed mood may decrease appetite and should be managed with counseling and antidepressants if indicated. Mirtazapine and olanzapine are useful agents for both depression and nausea.[34] A small single-arm trial of mirtazapine in nondepressed patients with CACS produced weight gain of 1 kg or greater in about one-quarter of participants within 4 weeks.[35,36] There are no consistently effective therapies for dysgeusia; however, a trial of zinc sulfate may be justified[37,38] because this supplement has few side effects in comparison to dronabinol, which is also shown to have benefit for chemosensory perception.

PHARMACOLOGIC INTERVENTIONS
Current Agents
Progestational agents. Systematic reviews indicate that megestrol acetate (MA) plays a role in CACS by increasing appetite and body weight compared to placebo.[39-41] However, these improved outcomes found in a minority of patients should be weighed against potentially serious side effects and a failure to show better quality of life compared to other interventions.[42] In addition, the weight gain MA-induced weight gain may be predominantly fat or fluid, rather than muscle.[43]

An updated Cochrane review in 2013[42] evaluated 35 trials (23 with cancer), including 928 patients with gastrointestinal or pancreatic cancer. Approximately one in four patients taking MA for cachexia (e.g., to treat cancer or AIDS) had an increase in appetite, while one in 12 experienced weight increase. Safety was evaluated in 3,180 patients. Dyspnea, edema, impotence, and thromboembolic phenomena were more common in patients taking MA, and deaths were increased, especially with higher doses. Since the median treatment duration was 8 weeks and follow-up length was short, the authors suggest adverse events may become even more relevant with prolonged use. Although some earlier studies showed improvement in fatigue as a secondary endpoint,[44,45] there are concerns prolonged suppression of gonadal and adrenal function by MA could exacerbate symptoms such as fatigue and poor libido.[46] Symptomatic adrenal suppression may be particularly problematic in pediatric patients with cancer, and stress-dose hydrocortisone is suggested for patients with acute illness or undergoing surgery.[47]

Because of the increased risk for mortality and thromboembolism, patients should be informed of the potentially serious side effects. MA should be reserved for patients placing a high priority on improved appetite, since MA may have an

antianabolic effect by decreasing muscle size.[48] Given that increased mortality is associated with higher doses of MA, it may be prudent to start at lower doses and monitor response. The optimal dose for weight gain is more than 400 mg/day, although improvements in appetite have been reported at 160 mg/day[4].

Corticosteroids. Although small randomized trials have shown corticosteroids improve symptoms of anorexia and fatigue,[49,50] only recently have two randomized, placebo-controlled trials confirmed their efficacy. In patients with advanced cancer (predominantly head and neck or gastrointestinal tumors), 4 mg dexamethasone twice daily for 14 days significantly improved fatigue (p = 0.008) and anorexia (p = 0.013) compared to placebo, with similar adverse events.[51] Notably, the physical domain of health-related, rather than the psychologic, quality of life improved. A prior positive trial in advanced gastrointestinal cancers had speculated the benefits of corticosteroids were largely caused by mood elevation.[17] A second recent study compared 7 days of 16 mg methylprednisolone twice daily to placebo and similarly showed improvements in fatigue and anorexia but no difference in the primary outcome of pain intensity.[52]

Despite improvement in appetite and fatigue in the short term, no studies have demonstrated any benefit on LBM, and prolonged use can cause proximal myopathy.[53] Although dexamethasone is considered preferable over other corticosteroids because of its lower mineralocorticoid effect, common toxicities include candidiasis, edema, cushingoid changes, depression, and anxiety.[54] Based on recent placebo-controlled clinical trials and the rapid onset of effect, dexamethasone seems most appropriate for short-term use in patients near the end of life.

Cannabinoids. Cannabinoids such as dronabinol and nabilone are approved for chemotherapy-related nausea in patients not responding to conventional antiemetics.[55] Dronabinol is also approved for treatment of anorexia in patients with AIDS,[56] but unfortunately, the evidence for any benefit in cancer cachexia is very limited. A multicenter randomized trial of 289 patients with advanced cancer compared the effects of cannabis extract delta-9-tetrahydrocannabinol (2.5 mg twice daily) and placebo on appetite and quality of life.[57] Consistent with other symptom intervention studies, there was a significant placebo effect and improved appetite in all three groups but no differences between the groups (p > 0.15). A lack of intrapatient dose escalation may be considered a limitation; however, the dose was based an earlier phase II study showing a higher risk of adverse psychotropic effects and dropouts in patients taking higher doses of dronabinol (5 vs. 2.5 mg).[58]

A multicenter randomized controlled trial (RCT) of 469 patients compared MA and dronabinol combination therapy to either agent alone for appetite stimulation in patients with lung or gastrointestinal cancer.[59] MA was superior to dronabinol alone, and combination therapy did not provide any additional benefit. Despite the consistently negative results in large trials, a recent single RCT showed that dronabinol improved taste and protein consumption in patients with cancer who had dysgeusia.[60]

Fish oil or eicosapentanoic acid. Despite eicosapentanoic acid (EPA) showing initial benefits for CACS and fatigue in patients with pancreatic cancer,[61] three systematic reviews found insufficient evidence for EPA in the management of cancer cachexia.[62-64] Although no serious adverse effects were reported, abdominal discomfort, belching, nausea, and diarrhea often affected quality of life. More recently, there is renewed interest in fish oil after two small RCTs showed improved weight and muscle mass in patients with non–small cell lung cancer (NSCLC) at initiation of first-line chemotherapy.[65,66]

Thalidomide. A recent Cochrane review of thalidomide in cancer cachexia found insufficient evidence for clinical practice.[67] Unfortunately, the review follows a study in patients with esophageal cancer showing no benefit and poor tolerability to thalidomide,[68] despite earlier trials in pancreatic[69] and esophageal cancer[70] that found improvements in LBM and minimal side effects after 4 weeks of 200 mg/day. More recently a phase II trial found improved appetite and minimal side effects with doses of 50 and 100 mg.[71] More trials are probably warranted; however, other studies of thalidomide have experienced difficulty in patient accrual.[72]

New Agents
Despite a number of promising interventions on the horizon, enobosarm and anamorelin are the only agents completing phase III RCTs.

Androgens. Hypogonadism is common in male patients with cancer and is associated with increased symptom burden including fatigue, anorexia, and diminished libido.[41-45] Although testosterone replacement has improved muscle mass and strength in HIV-positive men,[46] it has not been studied in large, RCTs for patients with cancer. A preliminary, double-blind, placebo-controlled trial of testosterone replacement in men with advanced cancer who had hypogonadism showed significant improvement in fatigue after 10 weeks (p = 0.003) but no effect on appetite or weight.[47]

Selective androgen receptor modulators theoretically produce greater anabolic effects with fewer side effects such as prostatic hypertrophy. A phase II RCT of enobosarm for patients with advanced cancer who had cachexia found increased LBM and physical function compared to baseline with minimal side effects.[73] Preliminary results from a phase III placebo-controlled trial showed an increase in LBM (p = 0.036) in patients with NSCLC on enobosarm treated with platinum plus taxane.[74] Physical function as assessed by stair-climb power was not significantly better in patients receiving enobosarm. Final results are awaited.

Ghrelin and ghrelin mimetics. Ghrelin, an orexigenic hormone, enhances appetite and food intake in humans. A phase

II RCT of ghrelin in patients with advanced cancer showed improved appetite and decreased fat loss with higher doses[50]; however, its development for CACS is hindered by the subcutaneous mode of administration and daily frequency. Because ghrelin has the potential for increasing insulin-like growth factor 1,[75] which could theoretically cause tumor progression, the initial efficacy and safety from early studies should be confirmed in large RCTs. An oral ghrelin mimetic anamorelin has made the furthest progress toward approval thus far, after early-phase trials showed increased food intake, appetite, and LBM in patients with cancer.[76] In addition, a pooled analysis of two phase II trials confirmed the benefits and few adverse effects of 12-week therapy. An encouraging preliminary report from the multicenter phase III trials suggests muscle mass (p = 0.0001) and appetite are improved in NSCLC.[77]

Myostatin and proinflammatory cytokine inhibitors. Myostatin is an extracellular cytokine that negatively regulates muscle mass.[54] The results of early-phase clinical trials are awaited following promising animal studies that showed tar-geting the myostatin pathway reversed muscle wasting, increased grip strength, stimulated appetite, and prolonged survival, independently of tumor progression.[78,79]

Few recent clinical trials have targeted proinflammatory cytokines, except for a phase I trial of a mAB against interleukin alfa-1 that showed a median weight gain of 1 kg from baseline and no dose-limiting toxicities.[80]

Multimodal therapy for the cancer anorexia-cachexia syndrome. Even though new single agents show potential for improving outcomes, a more effective approach might be simultaneous, multifaceted therapy targeting the different mechanisms contributing to CACS (Fig. 4).[81] Several studies have used a combination of pharmacologic agents for CACS.

A progestin in combination with an EPA, L-carnitine, and thalidomide significantly increased appetite, LBM (p = 0.007), and spontaneous physical activity, although there was no placebo arm.[82] Beta blockers[83] and insulin[84] have also been used as multimodality therapy in combination with nonsteroidal anti-inflammatories (NSAIDs), showing bene-

FIGURE 4. A Proposed Model for Management of Cancer Anorexia-Cachexia Syndrome
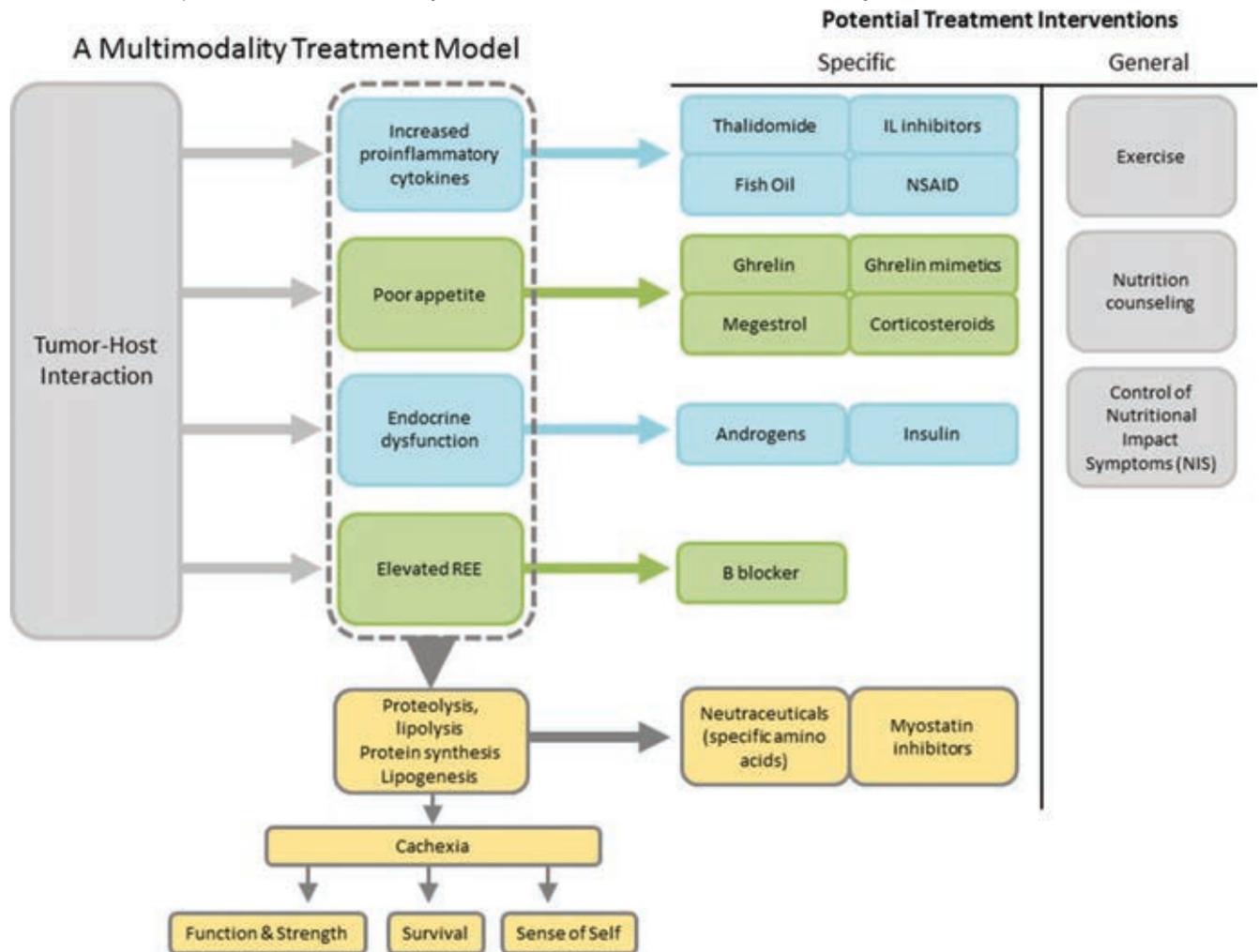
Abbreviations: REE, rested energy expenditure; NSAID, nonsteroidal anti-inflammatory.

fits in reducing elevated resting energy expenditure and attenuation of weight loss and also improvements in survival (p = 0.03). Although NSAIDs have been combined with other agents and have demonstrated improvement in some clinical outcomes, a systematic review concluded that the risk of side effects and insufficient evidence suggest NSAIDs should be restricted to clinical trials.[85]

CONCLUSION

Because the causes of muscle wasting and poor caloric intake in patients with CACS are multifactorial, a comprehensive multidimensional approach using pharmacologic and non-pharmacologic interventions is most likely to be effective in reversing or stabilizing weight loss and muscle wasting. Ideally, treatment should be individualized, taking into account the patient's overall condition, the principal mechanisms of their weight loss, and their goals of care. New anticachexia agents have shown promise in preclinical and early-phase studies, but their efficacy and safety need to be confirmed in larger phase III RCTs. Clearly there is an unmet need for an effective pharmacologic agent, and even though we now have several promising candidates, any specific anticachexia intervention would still need to be incorporated into a multimodality approach.

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GASTROINTESTINAL (NONCOLORECTAL) CANCER

The Many Faces of Neuroendocrine Cancers

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The Spectrum of Neuroendocrine Tumors: Histologic Classification, Unique Features and Areas of Overlap

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OVERVIEW

Neuroendocrine neoplasms are diverse in terms of sites of origin, functional status, and degrees of aggressiveness. This review will introduce some of the common features of neuroendocrine neoplasms and will explore the differences in pathology, classification, biology, and clinical management between tumors of different anatomic sites, specifically, the lung, pancreas, and prostate. Despite sharing neuroendocrine differentiation and histologic evidence of the neuroendocrine phenotype in most organs, well-differentiated neuroendocrine tumors (WD-NETs) and poorly differentiated neuroendocrine carcinomas (PD-NECs) are two very different families of neoplasms. WD-NETs (grade 1 and 2) are relatively indolent (with a natural history that can evolve over many years or decades), closely resemble non-neoplastic neuroendocrine cells, and demonstrate production of neurosecretory proteins, such as chromogranin A. They arise in the lungs and throughout the gastrointestinal tract and pancreas, but WD-NETs of the prostate gland are uncommon. Surgical resection is the mainstay of therapy, but treatment of unresectable disease depends on the site of origin. In contrast, PD-NECs (grade 3, small cell or large cell) of all sites often demonstrate alterations in P53 and Rb, exhibit an aggressive clinical course, and are treated with platinum-based chemotherapy. Only WD-NETs arise in patients with inherited neuroendocrine neoplasia syndromes (e.g., multiple endocrine neoplasia type 1), and some common genetic alterations are site-specific (e.g., *TMPRSS2-ERG* gene rearrangement in PD-NECs arising in the prostate gland). Advances in our understanding of the molecular basis of NETs should lead to new diagnostic and therapeutic strategies and is an area of active investigation.

Neuroendocrine neoplasms are a diverse group of neoplasms. Although these share certain pathologic features regardless of where they arise, they have largely been studied and classified in an organ-specific manner (which has led to a variety of different terminological variations) and their grading and staging remain site specific. Nonetheless, conceptual commonalities cross organ boundaries. This review will introduce some of the common features of neuroendocrine neoplasms and will also explore the differences in pathology, classification, biology, and clinical management between tumors of different anatomic sites, specifically the lungs, pancreas, and prostate.

PATHOLOGIC CONCEPTS IN NEUROENDOCRINE TUMORS

The concept of neuroendocrine differentiation in tumors can be defined as the secretion into the bloodstream of bioactive substances, usually peptide hormones or bioamines, by the neoplastic cells. The histologic similarity of the cells composing many neuroendocrine neoplasms and non-neoplastic neuroendocrine cells suggests that the tumors may arise from these mature counterparts. Although this concept is likely

overly simplistic even in the case of WD-NETs, which bear the closest resemblance to their normal cell counterparts. Pathologically, neuroendocrine differentiation has come to be defined as architectural and cytological patterns reminiscent of non-neoplastic neuroendocrine cells (such as a nesting or trabecular growth pattern and coarsely stippled nuclear chromatin) and the production of characteristic neurosecretory proteins that can be detected by immunohistochemistry. These include most importantly chromogranin A and synaptophysin, although some authorities accept the expression of CD56 (neural cell adhesion molecule or even neuron specific enolase (NSE) as adequate evidence of neuroendocrine differentiation.[1-3] However, NSE has been widely questioned as a neuroendocrine marker, based on the lack of specificity. Thus, in practice, WD-NETs are usually readily recognizable as having neuroendocrine differentiation based on their routine histologic features, and proof can be obtained with universally available immunohistochemical stains. The historic terms for WD-NETs was a carcinoid tumor or, in the pancreas, an islet cell tumor, although recent practice in the gastroenteropancreatic system has been to replace these terms with NET to avoid the connotation that a carcinoid tumor is a benign neoplasm.[1-3]

In addition to WD-NETs, which closely resemble non-neoplastic neuroendocrine cells, there also exist poorly differentiated neuroendocrine neoplasms, which are high grade carcinomas that exhibit neuroendocrine differentiation. These neoplasms also have characteristic histologic features (some of which are shared with WD-NETs) and they typically express the same general neuroendocrine markers described above, albeit less intensely and in fewer of the tumor cells. PD-NECs are usually classified as a small cell carcinoma or large cell neuroendocrine carcinoma (LCNEC), variants which are distinguished based on the cell size and specific nuclear morphology.[4] The histologic features of small cell carcinoma are sufficiently distinctive and can often be diagnosed without the need to demonstrate neuroendocrine differentiation by immunohistochemistry, whereas LCNEC must demonstrate immunexpression in at least one neuroendocrine marker to distinguish them from poorly differentiated carcinomas of an exocrine type (e.g., poorly differentiated adenocarcinoma or large cell undifferentiated carcinoma). PD-NECs are primarily distinguished from WD-NETs by having a substantially higher proliferative rate, although there are many other differences.

Despite sharing neuroendocrine differentiation and certain histologic features associated with the neuroendocrine phenotype, accumulating evidence demonstrates that, in most organs, WD-NETs and PD-NECs are actually two very different families of neoplasms.[4] They are etiologically different in some organs, and only the WD-NETs typically arise in patients with neuroendocrine neoplasia syndromes, such as MEN1 or von Hippel Lindau syndrome. The WD-NETs are variably aggressive, but most are relatively indolent with a

natural history that can evolve over many years or decades, whereas PD-NECs are uniformly highly aggressive.[5] PD-NECs, especially small cell carcinomas, exhibit marked but transient sensitivity to platinum-based chemotherapy, whereas WD-NETs are usually unresponsive to platinum and other cytotoxic chemotherapy regimens.[6,7] Also, PD-NECs often arise in association with exocrine-type precursor lesions or are combined with elements of adenocarcinoma or squamous cell carcinoma, though these associations are extremely rare in WD-NETs. Furthermore, individual tumors containing a combination of both WD-NET and PD-NEC are nearly nonexistent. Finally, emerging genetic data generally demonstrate distinct molecular alterations in these two neuroendocrine neoplasm families. Although some alterations are specific to the site of origin (discussed later), WD-NETs lack alterations in genes such as *Rb* and *TP53* that are commonly found in PD-NECs.

Although terminology and classification systems vary by organ (Table 1), the distinction between WD-NETs and PD-NECs applies in most organs.[2,8] Prognostic stratification based on grading has also been developed for most anatomic sites, and usually it is largely the proliferative rate that defines the grade.[9] Proliferative rate is determined by counting mitotic figures (usually expressed as the number 10 in high power microscopic fields or 2 mm^2) or, in some locations, by calculating the percent of tumor cells immunolabeling for the proliferation marker Ki67 (the Ki67 index). The entire group of neuroendocrine neoplasms is divided into three grades, with the low and intermediate grades (grade 1 and 2) being WD-NETs, and the high grade (grade 3) group generally consisting of PD-NECs.[2] Recently the grading parameters for neuroendocrine neoplasms of the entire gastrointestinal (GI) tract and pancreas have been unified, such that a single system proposed by the European Neuroendocrine Tumor Society (ENETS)[10,11] and endorsed by the World Health Organization (WHO)[12,13] is now widely used for this group of neoplasms (Table 2). In the thorax, a different WHO-accepted system has been in place for many years and is maintained for neuroendocrine neoplasms of the lung and thymus (Table 3).[14] For organs outside of these sites, various systems exist that largely draw on the thoracic or gastroenteropancreatic proposals. Details about each system are described later in the text. It should be emphasized that the classification and grading systems for all neuroendocrine neoplasms are being reviewed continuously, and new data are emerging that may suggest a need to modify the specific proliferation rate cut-points used for grading. Also, distinctive features specific to each site of origin are emerging, and many other potential prognostic factors are being evaluated. Thus, the ultimate assessment of prognosis will likely involve a grading scheme that will evolve with more experience and will be integrated with other prognostic data. A noteworthy advance was the inclusion of all neuroendocrine neoplasms in the American Joint Committee on Cancer (AJCC) staging system in 2009, some being staged using the same parameters as exocrine carcinomas of the same organ, others having unique NET-specific staging systems.[15]

KEY POINTS

- Neuroendocrine neoplasms are a diverse in terms of sites of origin, functional status, and degrees of aggressiveness.
- Despite sharing neuroendocrine differentiation and histologic evidence of the neuroendocrine phenotype, accumulating evidence suggests that in most organs, well-differentiated neuroendocrine tumors (WD-NETs)s (grade 1 and grade 2) and poorly differentiated neuroendocrine carcinomas PD-NECs (grade 3) are two very different families of neoplasms.
- WD-NETs arise in the lungs and throughout the gastrointestinal tract and pancreas; WD-NETs of the prostate gland are uncommon.
- Surgical resection is the mainstay of therapy for WD-NETs; treatment of unresectable disease depends on the site of origin.
- PD-NECs of all sites often demonstrate *P53* mutations and loss of *Rb*, exhibit an aggressive clinical course, and are treated with platinum-based chemotherapy.
- PD-NECs of the prostate should be suspected in patients who develop rapid progression in the setting of a disproportionately low prostate specific antigen; *TMPRSS2-ERG* gene rearrangement (present in 50% of patients) distinguishes PD-NECs of the prostate from small cell carcinomas of other primary sites.

TABLE 1. Classification of Neuroendocrine Neoplasms of the Lung, Pancreas, and Prostate

Differentiation	Grade	Lung	Pancreas	Prostate
Well differentiated	Low grade	Carcinoid tumor	Well-differentiated neuroendocrine tumor, grade 1	Carcinoid tumor*
	Intermediate grade	Atypical carcinoid tumor	Well-differentiated neuroendocrine tumor, grade 2	
Poorly differentiated	High grade	Small cell carcinoma	Poorly differentiated neuroendocrine carcinoma, grade 3; small cell carcinoma	Small cell carcinoma
		Large cell neuroendocrine carcinoma	Poorly differentiated neuroendocrine carcinoma, grade 3; large cell neuroendocrine carcinoma	Large cell neuroendocrine carcinoma
Combined	High grade	Combined small cell carcinoma (with adenocarcinoma or squamous cell carcinoma)	Mixed ductal neuroendocrine carcinoma (small cell carcinoma)	Mixed neuroendocrine carcinoma-acinar adenocarcinoma (small cell carcinoma)
		Combined large cell neuroendocrine carcinoma (with adenocarcinoma or squamous cell carcinoma)	Mixed ductal neuroendocrine carcinoma (large cell neuroendocrine carcinoma)	Mixed neuroendocrine carcinoma-acinar adenocarcinoma (large cell neuroendocrine carcinoma)
				Adenocarcinoma with Paneth cell-like neuroendocrine differentiation**

*Due to their rarity in the prostate, carcinoid tumors have not been divided into low and intermediate grades.

**Adenocarcinoma with Paneth cell-like neuroendocrine differentiation contains well-differentiated neuroendocrine cells, but the entity is included in the high-grade category because its biology is based on the adenocarcinoma component. These are not poorly differentiated neuroendocrine carcinomas in the family of small cell carcinomas or large cell neuroendocrine carcinomas.

An important subset of neuroendocrine neoplasms exhibits inappropriate secretion of one or more bioactive hormones, causing distinctive paraneoplastic syndromes, such as carcinoid syndrome, Cushing syndrome, and Zollinger-Ellison syndrome. The clinical picture of patients with these functional neuroendocrine tumors can be dominated by the paraneoplastic symptoms, which creates challenges in management unique to each tumor. Also, certain functional tumor types have a characteristic prognosis, such as the low rate of malignant behavior in pancreatic insulinomas. Although it is important to recognize functional tumors, the definition of these entities requires the presence of the corresponding clinical syndrome. Therefore, detection of specific hormones by immunohistochemistry is rarely useful in the pathologic characterization of neuroendocrine tumors.[1]

PATHOLOGIC APPROACH TO NEUROENDOCRINE TUMORS OF SPECIFIC ANATOMIC SITES
Pancreatic Neuroendocrine Tumors
Pancreatic neuroendocrine tumors (PanNETs) are well-differentiated NETs arising within the pancreas and include an array of functional types, including nonfunctional Pan-

TABLE 2. ENETS/WHO Grading System for Pancreatic Neuroendocrine Neoplasms

Tumor Grade	Definition
Low grade (grade 1)	< 2 mitoses/10 HPF, AND Ki67 index < 3%
Intermediate grade (grade 2)	2-20 mitoses/10 HPF, OR Ki67 index 3-20%
High grade (grade 3)	> 20 mitoses/10 HPF OR Ki67 index > 20%

Abbreviations: ENETS, European Neuroendocrine Tumor Society; WHO, World Health Organization; HPF, high power microscopic fields.

NETs, which are now the most prevalent type.[16] PD-NECs (small cell carcinoma and LCNEC) also arise in the pancreas but are rare. PanNETs can range from small (0.5 cm, by definition the size separating a PanNET from a neuroendocrine microadenoma), circumscribed, organ-confined tumors with a very low risk for aggressive behavior to large, necrotic, highly infiltrative malignancies.[17] The histologic patterns are usually typical of WD-NETs, but many morphologic variants exist that can cause confusion for other neoplasms. Such variants include, clear cell, oncocytic, glandular, pleomorphic, and rhabdoid morphologies.[18,19] The WHO classification system for PanNETs is the same for other neuroendocrine neoplasms of the GI tract (Table 2) and relies exclusively on the proliferative rate to separate grade 1, 2, and 3 neoplasms, the last group largely representing the PD-NECs.[8,20,21] A number of studies have validated the recommendation that both mitotic rate and Ki67 index be used to determine the grade, and that the region with the highest proliferative rate (hot spot) should be used to define the Ki67 index.[22] Also, in cases with grade discordance between the two proliferation measures, the higher grade should be assigned.[23,24] Grading based on biopsy samples remains complicated by heterogeneity within well-differentiated PanNETs, between the primary and metastases, and even among different metastatic sites.[22,25] Tumor stage and growth rate (for patients with distant metastases) observed on cross-sectional imaging are also helpful to predict the prognosis. A variety of other predictive markers have been evaluated, including immunohistochemical labeling for CD117, cytokeratin 19, CD99, CD44, p27, progesterone receptor, and PTEN, but none of these is routinely used in practice.[26]

The molecular alterations in PanNETs have been better characterized recently as a result of the completion of whole-

TABLE 3. IASLC/WHO Grading System for Pulmonary Neuroendocrine Neoplasms

Neoplasm	Morphology	Mitoses	Necrosis	Immunohistochemistry
Typical carcinoid tumor	Polygonal cells arranged in nested or trabecular patterns	< 2 per 10 HPF	Absent	Chromogranin, synaptophysin, CD56 (supportive, but not required)
Atypical carcinoid tumor	Polygonal cells arranged in nested or trabecular patterns	2-10 per 10 HPF	Present, usually punctate	Chromogranin, synaptophysin, CD56 (supportive, but not required)
Large cell neuroendocrine carcinoma	Large cells, moderate cytoplasm, round nuclei, frequent nucleoli	> 10 per HPF	Present, usually extensive	Chromogranin, synaptophysin, CD56 (at least one required)
Small cell carcinoma	Small cells, scant cytoplasm, fusiform nuclei, no nucleoli	> 10 per HPF	Present, usually extensive	Chromogranin, synaptophysin, CD56 (supportive, but not required)

Abbreviations: IASLC, International Association for the Study of Lung Cancer; WHO, World Health Organization; HPF, high power microscopic fields.

exome sequencing studies.[18] Well-differentiated PanNETs differ substantially from pancreatic ductal adenocarcinomas, which lack frequent alterations in *KRAS, TP53, CDKN2A*, and *SMAD4*. Instead, there are alterations in chromatin remodeling genes, such as *MEN1, DAXX*, and *ATRX*.[27] Additionally, alterations in members of the mTOR pathway are seen. Potential therapeutic targets can be proposed for PanNETs based on these alterations. Both *MEN1* and mTOR pathway alterations may be expected as a result of the occurrence of PanNETs in patients with *MEN1*, von Hippel-Lindau, neurofibromatosis-1, and tuberous sclerosis syndromes. PD-NECs of the pancreas have different molecular alterations from PanNETs, including common *TP53* and *Rb* mutations, as well as less frequent alterations in *KRAS* and *CDKN2A*.[28] These findings demonstrate the genetic distinction between the well differentiated and poorly differentiated families of pancreatic neuroendocrine neoplasms.

In terms of predicting response to specific therapy, there are few well-established biomarkers. Loss of expression of MGMT or methylation of its promoter can predict sensitivity to temozolomide.[29] In theory, inactivation of the mTOR pathway should also correlate in the response to mTOR inhibitor therapy, but this is a complex pathway with multiple positive and negative regulators, and a simple biomarker of pathway activation status has not been developed.[30,31]

Pulmonary Neuroendocrine Tumors

The classification of neuroendocrine neoplasms in the lung has been established for many years and, in many ways, represents the standard against which other neuroendocrine tumor families are judged (Table 3).[14] Well-differentiated NETs in the lung (and thymus) are still referred to as carcinoid tumors, with the designation of atypical carcinoid denoting the intermediate grade tumor. The high grade entities are the PD-NECs, small cell lung carcinoma (SCLC), and LCNEC.[32-34] Although a relatively new entry in the WHO classification, LCNEC received various designations in the past. In resected specimens, the morphology is typically neuroendocrine (trabecular pattern, rosettes, etc.), but the cells are larger than SCLC, with abundant cytoplasm and prominent nucleoli. Immunohistochemistry (IHC) confirmation with labeling for chromogranin, synaptophysin, or CD56 is required (Table 3). Important differential diagnostic consid-

erations include, large cell carcinoma with nuclear envelope (NE) morphology (which displays the typical NE morphology, but lacks IHC labeling for neuroendocrine markers) and large cell carcinoma with NE differentiation (which lacks NE morphology, but nonetheless expresses NE markers by IHC). Both of these entities should be approached clinically as a non–small cell lung cancer (NSCLC), as opposed to LCNEC, which is managed similarly to SCLC. Although the general concept of three grades and a separation between well-differentiated and poorly differentiated entities is the same as it is for the pancreas and GI tract, there are some subtle differences in the parameters for classification. Unlike in the GI and pancreatic NETs, the proliferative rate in the thoracic NETs is determined solely based on the mitotic rate. There are studies showing a positive correlation with the Ki67 index, and a formal classification of lung NETs that incorporates Ki67 has been proposed, but to date, the official WHO classification remains based only on mitotic rate.[35] However, the presence of necrosis is included, as either necrosis or an elevated mitotic rate can define a WD-NET as an atypical carcinoid tumor. Another difference is the threshold of the proliferative rate that separates intermediate grade (atypical carcinoid) from high grade (PD-NEC; small cell carcinoma or LCNEC). In the GI tract and pancreas, more than 20 mitoses per 10 high-power field (HPF) are needed, whereas in the lung, 10 mitoses per 10 HPF are sufficient to categorize a neoplasm as high grade.

As in other anatomic sites, pulmonary neuroendocrine neoplasms actually constitute two families that may not be closely related.[36] Carcinoid tumors, which can be central or peripheral in the lung, usually arise in nonsmokers and can occur in the setting of MEN1. They may also be associated with hyperplasia of pulmonary neuroendocrine cells, and they are usually not combined with adenocarcinoma or squamous cell carcinoma.[37] The PD-NECs, in contrast, are closely linked to tobacco use and commonly (up to 30%) contain elements of adenocarcinoma or squamous cell carcinoma. Such tumors are designated as combined neuroendocrine carcinomas. Finally, individual neoplasms containing both carcinoid tumor and PD-NEC are almost nonexistent. Molecular data further support the separation of carcinoids from PD-NECs. The latter commonly exhibit *TP53* and *Rb* mutations,[38,39] whereas carcinoid tumors lack these changes and instead (like pancreatic WD-NETs) have alterations in chro-

matin remodeling genes, such as *MEN1*, *PSIP1*, and *ARID1A*.[40]

Prostatic Neuroendocrine Tumors

In contrast to the lung and pancreas, where WD-NETs are relatively commonly encountered, the prostate almost never gives rise to true WD-NETs (carcinoid tumors). Individual case reports exist, but many such neoplasms may represent the more common manifestation of neuroendocrine differentiation in prostatic neoplasia and adenocarcinoma with neuroendocrine differentiation. A recent consensus group proposed a formal classification of prostatic neuroendocrine neoplasia.[41]

Conventional prostatic adenocarcinomas can exhibit neuroendocrine differentiation, but in the absence of a morphologically evident neuroendocrine component, focal immunohistochemically detected neuroendocrine differentiation is not thought to affect prognosis and it is not recommended to perform immunohistochemistry to search for it.[41] Prostatic adenocarcinoma with Paneth cell-like neuroendocrine differentiation is defined as a conventional prostatic adenocarcinoma containing morphologically evident neuroendocrine cells, which are typically highly granulated and resemble intestinal Paneth cells.[42] This phenomenon may be particularly marked following androgen deprivation therapy. The neuroendocrine cells lack an androgen receptor (AR) and have a well differentiated morphology, with bland nuclei and a low proliferative rate. When Paneth cell-like neuroendocrine differentiation is extensive, the tumor may resemble a true prostatic carcinoid tumor, but prostate specific antigen (PSA) expression is typically retained and elements of conventional adenocarcinoma are also usually identified. This pattern of differentiation is, if anything, a favorable prognostic sign, and the Gleason grade should be assigned based only on the pattern in the conventional adenocarcinoma elements. The rarest of all prostatic neuroendocrine neoplasms is a true carcinoid tumor, which can only be diagnosed when prostatic origin can be confirmed (as opposed to metastasis or direct extension from an adjacent organ) and Paneth cell-like neuroendocrine differentiation in a conventional prostatic adenocarcinoma is ruled out.[41] The absence of any adenocarcinoma component and negative immunostaining for PSA are required for the diagnosis.

The other types of prostate neuroendocrine neoplasms are PD-NECs, including small cell carcinoma[43,44] and LCNEC, the latter being very rare.[45] These tumors are often (but not always) positive for neuroendocrine markers (chromogranin, NSE, CD56, and/or synaptophysin) by IHC. As in other prostatic neuroendocrine neoplasms, AR expression is reduced or absent. Copy number loss of the tumor suppressors RB1 (85% to 90%)[46] and mutation of TP53 (50% to 60%) is shared with small cell carcinomas of other sites.[46,47] Notably, the combination of RB1 and TP53 alterations can drive small cell prostate cancer formation in mouse models.[48,49] In addition, PD-NEC of the prostate (NEPC) is associated with increased stem-like and neuronal signaling pathways (e.g., MYCN, ASCL1),[50] as evidenced by decreased expression of the master repressor of neuronal differentiation, RE1-silencing transcription factor (REST),[51] increased expression of cell cycle programs (e.g., AURKA, AURKB, PLK1),[47,50,52] and overexpression of the chromatin modifier DEK[53] and the polycomb complex gene, *EZH2*.[47,54] The role of these molecular alterations as diagnostic or predictive biomarkers remains to be determined.

These highly aggressive carcinomas can occur in pure form or—as in the lung, GI tract, and pancreas—they can be combined with elements of conventional adenocarcinoma. Mixed tumors are often heterogeneous with both AR positive and AR negative cells coexisting. Further demonstrating the relationship of these PD-NECs with conventional prostatic adenocarcinoma, some cases retain focal PSA immunoexpression. The prostate cancer-specific *TMPRSS2-ERG* gene rearrangement is detectable by fluorescence in situ hybridization (FISH) in approximately 50% of PD-NECs of the prostate (similar to the frequency in prostate adenocarcinomas) and distinguishes PD-NECs of the prostate from small cell carcinomas in other primary sites.[47,55]

Primary Site Determination in Neuroendocrine Neoplasms

In some clinical scenarios, it may be important to identify the site of origin of a neuroendocrine tumor presenting with metastatic disease. A variety of transcription factors can be helpful, although none are perfectly sensitive or specific on their own.[26] Thyroid transcription factor-1 (TTF1) labels pulmonary carcinoid tumors and is a good, if not insensitive, marker for WD-NETs provided a medullary thyroid carcinoma can be excluded. CDX2 is an intestinal lineage marker and generally stains only small bowel WD-NETs. Isl1 and PAX8 are positive in pancreatic WD-NETs and also, interestingly, label NETs of the rectum. A combination of these stains can supplement data from imaging studies in an attempt to identify the primary site. Defining the site of origin of a PD-NEC is more problematic, especially in the case of small cell carcinomas, which commonly express TTF1 as a primary in the lung, GI tract, pancreas, or prostate. In cases of small cell carcinoma of an unknown primary where prostate is suspected, *ERG* FISH is clinically indicated to support prostatic origin (though a negative test does not exclude it).

CLINICAL FEATURES AND MANAGEMENT OF PANCREATIC NEUROENDOCRINE TUMORS
Clinical Features

PanNETs arise in and around the pancreas and comprise approximately one-third of gastroenteropancreatic NETs (the remainder being traditional intestinal carcinoid tumors originating in the stomach and intestinal tract).[56] PanNETs account for approximately 1% to 2% of pancreatic tumors by incidence, but 10% by prevalence.[17,57,58] Interestingly, as with other NETs, the incidence of PanNETs is on the rise. It is unclear if this reflects improved diagnostic tools, an increased awareness of the disease, an aging population, or other factors.[59,60]

The majority of PanNETs (40% to 91%) are well-differentiated and nonfunctional, thus they are not associated with a clinical syndrome from hormone excess. Historically diagnosed at a late stage, advances in diagnostic imaging techniques (including endoscopic ultrasound) have facilitated detection of incidentally discovered small nonfunctional tumors, which now comprise up to 40% of newly diagnosed tumors.[61-63] Interestingly, asymptomatic secretion of peptides can be documented in 60% to 100% of nonfunctional tumors (e.g., chromogranin, pancreatic polypeptide, and others).[64] In contrast, a minority of patients (22% in a recent series) presents with a clinical syndrome stemming from hormone excess.[65] Insulin-producing tumors are the most common (90% of which exhibit benign behavior), followed by gastrinomas, glucagonomas, and other rarer syndromes.[64]

The initial work-up of a patient suspected to have a PanNET typically involves cross-sectional imaging with multiphasic CT or MRI to assess the primary tumor site and extent of disease. Endoscopic ultrasound, radiolabeled somatostatin receptor scintigraphy, and biochemical evaluations are recommended as clinically indicated.[64-66] Serum chromogranin A levels are elevated in 60% or more patients with a PanNET.[67]

Although indolent, PanNETs have malignant potential, as manifested by local invasion, lymph node involvement, and distant metastases. Most studies suggest that the risk of malignant behavior correlates with tumor size, as at least 50% of PanNETs recur or metastasize.[68] The presence of lymph node metastases also portends a worse prognosis in resected PanNETs (5-year survival is 49.4%).[69] Survival also depends on age, histologic grade, and functional status.[57] In contrast to other PanNETs, nearly all insulinomas are cured by complete resection.[64]

The etiology of PanNETs is largely unknown. Most tumors appear to be sporadic, but a small proportion of tumors arise in the setting of an inherited cancer syndrome (most commonly MEN1).[64] The potential for an accompanying inherited syndrome should always be considered, particularly if the patient has a compelling personal or family history, multifocal disease, a gastrinoma, or an insulinoma.[64]

Treatment

In addition to controlling tumor growth, it is critical to recognize the need for medical management of the hormone-excessive state in PanNETs. Somatostatin analogs (SSTa) are often employed for symptom control, but medications to control gastric acid hypersecretion and hypoglycemia are essential for patients with gastrinomas and insulinomas, respectively.[64,66] Of note, SSTa should generally be avoided in patients with insulinomas whose tumors test negative by somatostatin receptor scintigraphy.[66]

Patients with localized PanNETs are typically treated with surgical resection with regional lymph node dissection as there are no data to support neoadjuvant or adjuvant therapy. The optimal surgical technique depends on the location of the tumor. For some patients, enucleation may suffice (e.g., patients with insulinomas and incidentally detected small nonfunctional PanNETs).[70] The resultant lack of lymphadenectomy is a potential concern, however, as nonfunctional tumors that measure 10mm to 20 mm have a small but real risk of lymph node involvement.[66,70] On the other hand, several studies suggest that nonfunctional tumors that measure less than 10 mm may be safely observed in some cases.[66,71] Given the relatively indolent nature of the disease, patients with PanNET should be followed for recurrence for up to 10 years postresection.[66]

The treatment of advanced PanNETs has evolved dramatically in the last 5 years. Surgical resection of all known disease is recommended when feasible, although the data suggest that such operations are not curative.[66] The risk of recurrence after resection of NET liver metastases approaches 100% at 10 years in some series.[72,73] The role of cytoreductive surgery and/or ablation is more controversial, but is a consideration in select patients.

In patients with an unresectable disease, observation is an acceptable option in asymptomatic individuals with a low tumor burden and stable disease.[66] If systemic therapy is required, several targeted agents have proven cytostatic activity in PanNETs. Recent data suggest that biologically important subgroups may exist (e.g., those with *MEN1* or *DAXX/ATRX* mutations), but studies correlating mutations with a clinical outcome have been mixed.[74] Additional research is needed to identify valid biomarkers predictive of response to therapy in PanNETs. Octreotide delays progression in tumors of a midgut origin and is presumed to be active in PanNETs.[75] Patients with nonfunctional WD-NETs (including PanNETs) were included in the CLARINET study, in which patients were randomly selected to receive lanreotide or placebo.[76] Treatment with lanreotide improved progression-free survival (PFS; not reached vs. 18 months for placebo; hazard ratio 0.47; 95% CI, 0.30 to 0.73; p < 0.001), leading to approval for this indication. Peptide receptor radiotherapy with Lu^{177}- or Y^{90}-labeled SSTa also holds promise, but remains investigational for the treatment of PanNETs in the United States.[77]

The biologically targeted agents sunitinib and everolimus also delay tumor growth in progressive PanNETs and are approved for this indication.[30,78] Sunitinib is an oral multitargeted agent that inhibits vascular endothelial growth factor (VEGF) receptor signaling. In patients with progressive PanNET, treatment with sunitinib delays progression by approximately 6 months (median PFS 11.4 months vs. 5.5 months with placebo; p < 0.001).[78] The mTOR inhibitor everolimus also delays progression in patients with PanNETs (median PFS duration 11.0 months vs. 4.6 months with placebo, p < 0.001).[30] There are no data to guide the sequence of these agents, which have distinct side effect profiles and are characterized by stability, not shrinkage. Of note, although still considered investigational, preliminary results suggest that dual targeting of mTOR and VEGF signaling may be a means of inducing tumor regression, not just stability, in PanNET.[79]

The role of chemotherapy in PanNETs is evolving, but remains an option, particularly in patients with a progressive

disease and/or symptoms from tumor bulk. Streptozocin was approved for this indication more than 20 years ago.[80] However, subsequent studies have yielded conflicting results, raising questions about the optimal chemotherapy backbone in this disease.[81,82] Data from several small phase II studies have suggested that temozolomide-based regimens are active in PanNET, however, data from prospective randomized trials are lacking.[83] Combinations of targeted agents plus chemotherapy are also under study.[84]

In patients with PanNETs and a liver dominant disease, palliative liver-directed treatments (e.g., selective internal radiation therapy, hepatic arterial embolization, and hepatic arterial chemoembolization) are frequently employed.[85,86] The optimal timing and precise role of liver-directed therapy relative to the systemic agents that are U.S. Food and Drug Administration–approved is unclear.

PD-NECs of the pancreas are uncommon. When they occur, most are of the large cell type, metastatic at presentation, associated with a poor prognosis, and treated with platinum-based chemotherapy according to SCLC guidelines.[8]

CLINICAL FEATURES AND MANAGEMENT OF NEUROENDOCRINE TUMORS OF THE LUNG
Clinical Features

Carcinoid tumors, typical and atypical, account for approximately 1% to 2% of lung cancers and tend to have an indolent course.[59] Most lung carcinoids present with a central mass and symptoms secondary to airway involvement, such as cough, hemoptysis, dyspnea, or unresolved pneumonia. Carcinoid syndrome is rare in the absence of metastatic disease to the liver. A CT scan of the chest can suggest the diagnosis; and PET scans are usually not contributory. The diagnosis is typically made by bronchoscopy, except in peripheral lesions when a CT-guided biopsy is recommended.

On the other side of the NE spectrum, SCLC is more frequent (approximately 13% of all lung cancers), often advanced at presentation, and typically follows a more aggressive course.[87] A detailed discussion on the diagnosis and management of SCLC is beyond the scope of this article. Only one-fourth of patients present with limited stage SCLC (LD-SCLC) with disease confined to the chest and nodes (excluding contralateral hilar or contralateral supraclavicular nodes), whereas the majority of patients have extensive stage SCLC (ED-SCLC) or disease beyond the above definition at the time of the diagnosis.

The management of carcinoid tumors and SCLC across the NET spectrum has not changed appreciably in the past 2 decades. On the other hand, the diagnosis and treatment of LCNEC continues to generate considerable debate.[88] Important differences between SCLC and LCNEC include more frequent presentation of LCNEC as a peripheral mass and diagnoses in earlier stages.

Treatment
Carcinoid. The treatment of carcinoid tumors consists of surgical resection (including a nodal dissection) because of the frequent incidence of mediastinal involvement, particularly in atypical carcinoids.[89] The vast majority of patients with completely resected carcinoid tumors do not require adjuvant therapy. However, for patients with mediastinal node disease, the NCCN guidelines suggest consideration of treatment using chemotherapy and/or radiotherapy.[90] The efficacy of this intervention is unproven.[91] For patients with metastatic disease, chemotherapy with regimens used for SCLC is the mainstay of treatment. Unlike NE tumors of the GI tract, molecular-based therapies have not shown to be beneficial in carcinoid tumors, except for anecdotal case reports. The 5- and 10-year survival approaches 90% and 80% for typical carcinoids and approximately 70% and 50% for patients with atypical carcinoids, respectively.

SCLC. Combined chemotherapy and thoracic radiotherapy (TRT) followed by prophylactic cranial irradiation (PCI) is the recommended treatment for LD-SCLC and leads to a cure in approximately 15% to 25% of patients.[92] In ED-SCLC, chemotherapy is the primary treatment. PCI and consolidative chest radiotherapy prolong survival and should be discussed with patients who achieve a complete or a very good partial response to chemotherapy.[93] In contrast to NSCLC, targeted agents are not used in patients with SCLC, and immunotherapy is currently being explored.

LCNEC. The presence of a peripheral mass and discovery at an earlier stage contribute to the greater rate of surgical resection experienced by patients with LCNEC compared to those with SCLC, which rarely presents as a solitary peripheral nodule.[94] After resection, patients with LCNEC should receive adjuvant combined chemotherapy with platinum-etoposide regimens and TRT if the mediastinal nodes are positive. If unresectable at presentation, concurrent combined chemotherapy/TRT is the treatment of choice. Although little data exist to document the benefit of PCI in this disease, it should be considered in select patients.

CLINICAL FEATURES AND MANAGEMENT OF PROSTATIC NEUROENDOCRINE TUMORS
Clinical Features

In the majority of cases, neuroendocrine tumors of the prostate arise in the setting of concurrent or previously diagnosed conventional prostatic adenocarcinoma. Focal immunohistochemically detected neuroendocrine differentiation and Paneth cell morphology should be managed as prostate adenocarcinomas and carry a similar prognosis. PD-NEC, such as a small cell carcinoma, accounts for less than 1% of new prostate cancer diagnoses, but it more commonly arises as an androgen independent disease during clinical resistance to hormonal therapies.[95] Once NEPC develops, patients typically demonstrate an aggressive clinical course and poor overall survival.[95-97] Detection of patients developing NEPC is important, as these patients are less likely to respond to subsequent AR targeted therapies. However, diagnosis remains challenging because the clinical features associated

with AR independence and PD-NEC have only recently been recognized.

The incidence of NEPC is not well established because obtaining repeat biopsies in patients with metastatic prostate cancer has not been common practice. Autopsy series suggest PD-NEC may be present in up to 10% to 20% of men dying of metastatic castration-resistant prostate cancer (CRPC). Emerging data from the biopsies of metastases from patients with CRPC treated with the potent AR targeted therapies abiraterone or enzalutamide suggest the incidence may be rising.[98] This increased incidence could be a result of an increased recognition, patients living longer, or because of the effect of novel therapies. In a recent meta-analysis by Wang et al, which evaluated clinical outcomes of 123 patients with histologically confirmed NEPC that arose after a history of prostate adenocarcinoma, the median time of progression from adenocarcinoma to PD-NEC was 20 months and the median overall survival of patients with PD-NEC was 7 months.[99] Clinically, PD-NEC is associated with symptoms of accelerated disease progression often in the presence of visceral, lytic bone, or unusual sites of metastatic disease; a disproportionately low-serum PSA relative to the overall burden of disease; and a limited response to AR-targeted therapies.[52,96,97,100,101] Uncommonly, NEPC may be associated with an ectopic production of hormones (such as adrenocorticotrophic hormone [ADH], antidiuretic hormone, thyroxine, and with clinical manifestations of thyrotoxicosis), inappropriate ADH production, hypercalcemia, and/or adrenal hyperfunction. Elevated serum neuroendocrine markers (including chromogranin A, NSE, and/or carcinoembryonic antigen) may help support the diagnosis but can also sometimes be elevated in CRPC with adenocarcinoma histology.[102] If PD-NEC is suspected, a biopsy should be considered to confirm the diagnosis. The diagnosis and treatment of PD-NEC can be challenging, and assessment of the clinical context and additional pathologic review are often recommended before making treatment recommendations.

Treatment

Few patients with pure NEPC present with localized disease, and therefore there are limited data on treatment of patients with organ-confined disease. These patients are very likely to have occult metastatic disease not detected on a bone or CT scan, but PET scans may be useful in confirming localized disease.[103] For localized PD-NEC, a multimodality approach similar to SCLC should be considered, which consists of chemotherapy with concurrent or consolidative radiotherapy. Very limited data are available regarding the use of surgery in this clinical setting.

Chemotherapy is commonly used as front-line therapy for metastatic PD-NEC that either presents as de novo or occurs after therapy.[95,100] Since PD-NEC can show mixed or hybrid features (as described above with both PD-NEC and prostate adenocarcinoma components), androgen deprivation therapy is also often given either first or in combination with chemotherapy, depending on the clinical context. Platinum-based chemotherapy regimens (most often with cisplatin or carboplatin with either etoposide or taxane chemotherapy [docetaxel or paclitaxel]) are recommended for patients with aggressive clinical features and predominantly PD-NEC histology. In a phase II clinical trial of 38 patients with small cell prostate cancer treated with doxorubicin, cisplatin, and etoposide, Papandreou et al reported an objective response rate of 61%, although there were no complete responses.[104] This regimen was associated with greater toxicity as compared to cisplatin and etoposide alone, and there was no improvement in the median time to progression (5.8 months) and overall survival (10.8 months). Most recently, Aparicio et al defined a clinical diagnosis of anaplastic prostate cancer by one of seven aggressive clinical features (including PD-NEC) for inclusion into a phase II study of carboplatin and docetaxel (CD) followed by etoposide and cisplatin (EP) on progression.[105] In this study, 65.4% and 33.8% of patients were progression free after four cycles of CD and EP, respectively. Median overall survival was 16 months (95% CI, 13.6 to 19.0 months). There is no standard therapy after platinum chemotherapy, and patients are typically managed according to SCLC guidelines.

Special Considerations

Primary diagnostic challenge. Not all patients with aggressive androgen independent–CRPC demonstrate clear evidence of PD-NEC morphology on a metastatic biopsy.

Clinically aggressive tumors in the setting of a low PSA and poor clinical response to AR therapies (suggestive of AR independence) do not always demonstrate morphologic features of PD-NEC. This may be a result of disease heterogeneity and/or overlapping molecular features. Therefore, tumor morphology does not always predict clinical behavior. Chemotherapy including platinum is often considered, based on studies in anaplastic prostate cancer. The role of alternative AR therapies in this setting is not known.

Secondary diagnostic challenge. PD-NEC is not always androgen independent. At times, morphologic features or immunohistochemical profiles of metastatic tumors suggest PD-NEC, but AR expression and/or signaling are active.[106] These tumors are often either mixed or show hybrid features with both AR and neuroendocrine markers present. Clinically, these are less aggressive than most cases of PD-NEC, and patients are sometimes recommended for hormonal therapies. Future molecular markers to distinguish AR-driven CRPC from AR-independent disease will aid in patient selection for therapy.

CONCLUSION

Neuroendocrine neoplasms are a diverse group of neoplasms distinguished by site of origin, functional status, and degree of aggressiveness. Although a variety of pathologic features are shared, NETs have largely been classified in an organ-specific manner and their grading and staging remain site-specific. Nonetheless, several themes cross organ boundaries.

WD-NETs (grade 1 and 2) are relatively indolent (with a natural history that can evolve over many years or decades), closely resemble non-neoplastic neuroendocrine cells, and demonstrate production of neurosecretory proteins, such as chromogranin A and synaptophysin. Only WD-NETs arise in patients with inherited neuroendocrine neoplasia syndromes (e.g., MEN1). Surgery is the mainstay of therapy for WD-NETs, which are relatively unresponsive to chemotherapy (although several cytostatic agents have proven activity). In contrast, PD-NECs (grade 3) are uniformly highly aggressive, demonstrate a high proliferative rate, and are classified as small cell carcinoma or LCNEC. PD-NECs typically harbor molecular alterations distinctive from WD-NETs (leading to loss of Rb and P53 function), and some alterations are site-specific (e.g., *TMPRSS2-ERG* gene rearrangement in NEPC). PD-NECs exhibit marked but transient sensitivity to platinum-based chemotherapy and are usually metastatic at diagnosis. Although validated biomarkers of response are not yet available, advances in the understanding of the molecular basis of NETs may lead to new diagnostic and therapeutic strategies, and holds the promise of an individualized therapy.

Disclosures of Potential Conflicts of Interest

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GENITOURINARY CANCER

Beyond Tyrosine Kinase Inhibitor Therapy: Incorporating Immunotherapy and Metastasectomy into Renal Cell Carcinoma Management

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Challenging the Treatment Paradigm for Advanced Renal Cell Carcinoma: A Review of Systemic and Localized Therapies

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OVERVIEW

The current standard of care for the management of advanced renal cell carcinoma (RCC) revolves around systemic therapy with molecularly targeted agents. Over the last decade, a total of seven targeted drugs have been approved but, altogether, only exploit two molecular targets in this disease: the vascular endothelial growth factor (VEGF) axis and the mammalian target of rapamycin (mTOR). Introduction of these agents has markedly improved outcomes compared with those in the cytokine era, yet comparatively little progress has been made since registration of the first targeted therapeutics occurred 10 years ago. In this article, we review efforts to improve on this current treatment paradigm. We discuss novel targets in this disease and corresponding new agents under investigation. The article dedicates particular attention to targeted immunotherapeutics, which are rapidly emerging as a new category of interest in this disease. Last, we review current data supporting the use of surgical interventions to improve outcomes in patients with metastatic disease.

Targeted therapy for kidney cancer has revolutionized the management of metastatic disease in the last 5 years, but major challenges remain. First, these drugs typically control disease for approximately 9 months in fit patients in the first-line setting and for approximately 5 months in subsequent lines of therapy. As such, there is a clear scope for identifying new pathways and targets as well as better selection of patients for therapy. Second, a new generation of immunotherapy agents is in development; should these drugs be approved for use, their integration into current treatment paradigms requires investigation. Third, local therapy for metastatic disease plays a significant role in the management of metastatic kidney cancer and is associated with prolonged survival, despite the lack of a high-quality evidence base. We review here these three areas of clinical and scientific literature in kidney cancer in 2015.

NEW PATHWAYS AND TARGETS IN CLEAR CELL KIDNEY CANCER

Since the approvals of the multitargeted kinase inhibitors sorafenib and sunitinib and the mTOR inhibitor temsirolimus almost 10 years ago for the treatment of advanced kidney cancer, it could be argued that relatively little progress has been made with targeted therapy for this disease. A number of new, but similar, agents, such as pazopanib, axitinib and everolimus, have subsequently been approved. However, gains in efficacy, if any, have been modest compared with the efficacy of the earlier generation of agents, and sunitinib remains a standard of care for the first-line treatment of advanced disease in 2015. Furthermore, all of the approved targeted agents, with the exception of the anti–VEGF monoclonal antibody bevacizumab, are either mTOR inhibitors or multitargeted kinase inhibitors. Moreover, the multitargeted kinase inhibitors all inhibit at least one isoform of the VEGF receptor in addition to, sometimes, dozens of other targets. Notably, there is currently no strong evidence that any of the other targets inhibited by these agents is of therapeutic relevance in clear cell renal carcinoma.

Augmenting Anti-VEGF and mTOR Strategies

Two recent approaches to developing new agents for the treatment of kidney cancer have focused, first, on broader targeting of the phosphoinositide 3-kinase (PI3K)/mTOR signaling pathway and, second, on the evaluation of multitargeted kinase inhibitors and drug combinations that in addition to targeting the VEGF axis also target other putative drivers in advanced renal cell carcinoma (RCC) and potential mediators of resistance to VEGF inhibition (e.g., fibroblast growth factor receptor [FGFR] and c-MET).

Initial attempts to better target the mTOR signaling pathway have not met with success to date. For example, a small, randomized, phase II study of the dual pan-PI3K and TORC1/2 inhibitor apitolisib (GDC0980) versus everolimus in patients refractory to anti-VEGF therapy reported inferior

progression-free survival (PFS) for patients treated with apitolisib.[1] The results of further trials, such as those investigating the dual TORC inhibitor AZD2014 in comparison with everolimus, are awaited with interest.

Preclinical data have suggested that a number of targets may be relevant for resistance, both intrinsic and acquired, to anti-VEGF therapy in advanced kidney cancer. In this context, the phase III GOLD trial investigated the VEGF receptor (VEGFR) and FGFR inhibitor dovitinib compared with sorafenib in patients who had experienced failure of both VEGF- and mTOR-targeted therapy (i.e., in the third-line setting).[2] This trial showed activity for dovitinib, but the activity was not superior to that of sorafenib; as such, the trial was negative for its primary endpoint of PFS. A null hypothesis in interpreting the efficacy data from this trial is that the activity of dovitinib was a sole consequence of activity against the VEGF pathway and that the activity against FGFR was not relevant to efficacy, but this contention remains unproven.

A further target of recent interest in RCC is the tyrosine kinase c-MET. Analogous to the GOLD trial, the phase III METEOR trial is investigating the VEGFR and c-MET inhibitor cabozantinib in patients who have experienced failure of prior anti-VEGF therapy. However, even if cabozantinib has superior efficacy to everolimus in this setting, c-MET is not necessarily validated as a bona fide target in clear cell kidney cancer, given that cabozantinib also targets VEGF. It is noteworthy in this regard that two recent trials have shown superior efficacy for anti-VEGF therapy compared with mTOR-targeted therapy. Specifically, a phase III trial of sorafenib versus temsirolimus in patients in whom first-line therapy with sunitinib had failed[3] reported similar PFS in both arms, but overall survival (OS) was superior in the sorafenib arm. The reason for this is unclear. Furthermore, a randomized,

phase II trial of sunitinib versus everolimus in the first-line setting[4] of almost 500 patients reported a median PFS of 10.7 months for sunitinib versus 7.9 months for everolimus (hazard ratio [HR] 1.4; 95% CI, 1.2 to 1.8).

Combinations of Targeted Therapy in 2015

A further approach to try to improve outcomes of drug therapy in advanced RCC that has been investigated for a number of years is the combination of targeted therapies. Attempts of combining currently approved agents have not been successful and have resulted typically in excessive toxicity, the need to reduce drug doses, and no evidence of clinical benefit.[5-8] This approach remains of interest, nevertheless, and the results of a randomized, phase II trial (NCT01136733) comparing the combination of the multitargeted kinase inhibitor lenvatinib and everolimus with either agent alone are expected soon. Recognizing that von Hippel-Lindau (VHL) loss is essentially universal and, hence, that dependence on tumor neovascularization is omnipresent in clear cell RCC, several studies are exploring combinations of approved VEGF-targeted therapies with novel inhibitors of non-VEGF–mediated angiogenesis. Examples include the ongoing DART trial, a randomized, phase II study of axitinib plus the activin receptor-like kinase-1 (ALK1) – directed trap molecule dalantercept versus placebo (NCT01727336); this combination demonstrated favorable tolerability and encouraging activity in a recent phase I trial in RCC.[9] Similarly, the addition of the antiendoglin antibody TRC105 to standard therapy with axitinib is being evaluated in another randomized, placebo-controlled, phase II trial that is currently accruing (NCT01806064).

Challenges for Targeted Therapy in Advanced RCC

Perhaps the fundamental problem with improving outcomes with targeted therapy in advanced RCC is the lack of molecular predictive factors for selecting therapy and the consequent one-size-fits-all approach. This is in contrast to the use of targeted therapies to treat most other advanced malignancies, in which factors such as mutations in driver oncogenes (e.g., *BRAF* in melanoma) are used to select patients for appropriate therapy. A pertinent observation in this respect, though, is that clear cell renal carcinoma is characterized molecularly by aberrations in tumor suppressor genes rather than activating mutations in oncogenes, as in the melanoma example. The consequence of the loss of tumor suppressor genes in clear cell RCC is a pathologic dependence on signaling via the VEGF axis; to date, there is no way to measure this dependence in a way that is clinically useful in selecting systemic therapy. A related issue is whether or not a particular molecular target is relevant as a driver of the disease in an individual tumor. In many ways, it might be surprising if one target, such as c-MET or FGFR, was responsible for resistance to anti-VEGF therapy in the majority of patients. Thus, even if such targets are potentially relevant in some cases, it will remain difficult to make significant progress with targeted therapy in this disease if patients entering clinical trials are molecularly unselected.

KEY POINTS

- Since the advent of molecularly targeted therapy for the treatment of advanced renal cell carcinoma (RCC), further improvement in outcomes with subsequent approval of additional agents has been modest, at best.
- Two key strategies of developing novel agents have been (1) broader targeting of the phosphoinositide 3-kinase/mammalian target of rapamycin signaling pathway and (2) combined inhibition of other targets with vascular endothelial growth factor–directed therapies.
- Targeted immunotherapy with checkpoint inhibitors is rapidly emerging as a new class of agents in this disease. Ongoing studies test its utility alone and in combinations with approved agents.
- A growing body of data supports the use of metastasectomy to improve outcome in patients with metastatic RCC.
- Clinical and radiographic parameters could help optimize the selection of patients with metastatic disease for surgical intervention and should be validated prospectively.

Finally the issue of intratumor heterogeneity is potentially relevant for the further development of targeted therapy in kidney cancer.[10] A critical consideration is whether or not a particular molecular aberration is a driver of tumor progression at all tumor sites—that is, a truncal driver. To make a further analogy with melanoma, activating mutations in *BRAF* are truncal drivers in *BRAF*-mutant melanoma. That is, disease progression at primary and metastatic sites is driven by this aberration, and *BRAF*-targeted therapy results in disease regression, at least temporarily, in the vast majority of cases. Some data in clear cell renal carcinoma suggest that mutations in VHL may be the only bona fide truncal driver in this disease.[11] Other mutations, for example those in *SETD2* or *PBRM1*, may not be present at all tumor sites. This may be therapeutically relevant, because aberrations in the mTOR signaling pathway are relatively common in clear cell RCC, but the overall activity of mTOR inhibitors is less than that of anti-VEGF therapy. One possible explanation for this is that mTOR signaling aberrations are rarely truncal drivers. This contention, however, requires further study, particularly in characterizing the genomic architecture of the disease at metastatic sites.

Agents like cabozantinib may be approved in due course for the treatment of advanced RCC, and combination therapy remains of interest as an approach to treating this disease. Nevertheless, without molecular characterization of patients who have advanced RCC and clinical trials directed at resultant specific populations, it is difficult to see how the next decade will see the same progress in molecularly targeted therapy that we have witnessed in the last 10 years.

INTEGRATING IMMUNOTHERAPY INTO THE CURRENT TREATMENT PARADIGM IN ADVANCED RENAL CELL CARCINOMA

Immunotherapy has a longstanding history in the management of advanced renal cancer. Although monotherapy with interferon alfa largely has been abandoned since the introduction of targeted agents, high-dose interleukin-2 remains an approved standard in the first-line setting, albeit only utilized for a select subgroup of patients (as reviewed by McDermott et al[12]). Recently, a novel class of immunotherapeutics is rapidly gaining recognition for RCC and other diseases. These so-called checkpoint inhibitors interfere with inhibitory cell-cell interactions that suppress the tumor-directed T-cell response via molecules like cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and programmed death-1 (PD-1).

With a number of phase II and III trials underway, checkpoint inhibitors presently are being tested on their own and in combination with approved targeted agents. This growing body of clinical data, particularly around agents targeting PD-1 or its binding partner PD-ligand 1 (PD-L1), raises the question of how to integrate this class of agents into the present treatment paradigm for this disease.

Checkpoint Inhibitors in Advanced RCC: Monotherapy

Since the early 2000s, RCC drug development has chiefly revolved around inhibition of VEGF and mTOR, which relies on the sequential use of different agents targeting the same pathway in any given patient who has metastatic disease (e.g., following VEGF inhibition with another VEGF inhibitor). The advent of targeted immunotherapy may provide an opportunity to add a novel class of agents to this sequence of therapies.

Furthest in clinical development for metastatic RCC is the fully human IgG4 monoclonal antibody nivolumab (Bristol-Meyer Squibb, New York, NY), which targets PD-1. A dose-randomized, phase II study in patients pretreated with one to three prior antiangiogenic therapies was recently reported.[13] Objective response rates (ORRs) of approximately 20% and a median PFS of approximately 4 months were comparable to efficacy data for approved targeted agents in the pretreated space.[14,15] OS exceeded historic controls (median OS, approximately 25 months in the higher dose-levels versus approximately 15 months for approved targeted agents in pretreated patients). Such cross-trial comparisons are of limited value, but this marked difference in the reported OS may reflect longer-lasting immunomodulatory effects that may enhance the effectiveness of subsequent agents, particularly in the light of the modest PFS findings. This would argue in favor of using nivolumab maximally early, ideally first line, in a patient's course of disease. The sponsor has chosen to develop nivolumab for monotherapy in pretreated patients (with parallel development of combination strategies in first-line settings); a phase III trial that randomly assigned patients to nivolumab versus everolimus after one or two prior antiangiogenic therapies (NCT01668784) has completed accrual. The primary endpoint is OS, prompted by the phase II signal; this endpoint represents a paradigm shift for this disease, in which registration studies have typically pursued PFS as the primary endpoint.

It has been suggested that the antitumor effects of nivolumab and other compounds can extend beyond the end of treatment; anecdotally, a number of patients have not required further therapies for extended periods of time. For those patients who experience disease progression during treatment, however, it is unclear if and how immune modulation with checkpoint inhibitors affects effectiveness and tolerability of subsequent, nonimmunotherapy treatments. As the field's clinical experience with these compounds increases, it will be important to investigate these questions prospectively to optimize the clinical use of targeted immunotherapy.

There are no established biomarkers for the use of approved VEGF- and mTOR-directed agents, and patients are not selected for therapy on the basis of molecular features. With the introduction of a novel class of agents, the question of whether this paradigm should change has arisen. The significance of the expression of PD-L1 on tumor cells or tumor-infiltrating lymphocytes is best studied for PD-1 inhibition. With monotherapy, stronger expression levels appear to correlate with higher response rates, but patients who have

limited expression levels can still benefit from treatment.[13,16] The limitations of using immunohistochemistry as a biomarker chiefly lie in the dynamic nature of PD-L1 expression and in differences in tissue processing, among other differences. Recent data in melanoma revealed that neoantigen signatures, which are the results of acquired somatic mutations, can correlate with treatment effectiveness of CTLA-4 inhibition.[17] These data suggest that genomic profiling of the tumor tissue may prove useful as a predictive biomarker for checkpoint inhibitors.

Checkpoint Inhibitor Combinations

Concurrent blockade of PD-1 and CTLA4 is hypothesized to be complementary in regulating adaptive immunity. For RCC, this notion is supported by data from a phase I study combining nivolumab with the CTLA4-directed fully humanized monoclonal antibody ipilimumab in a heterogeneous group of 44 patients (80% pretreated).[18] A 45% ORR, with 80% of the responses ongoing at the time of report, prompted the sponsor to move straight into a phase III study (NCT02231749), which is presently ongoing. This trial is recruiting untreated patients with metastatic disease, who are randomly assigned 1:1 to receive the combination of nivolumab plus ipilimumab versus sunitinib on the comparator arm. With PFS and OS as the coprimary endpoints, the trial is designed to challenge the current treatment paradigm of a VEGF kinase inhibitor as the widely accepted standard of care in first-line settings. Note that the combination's unique toxicity profile frequently requires the use of systemic corticosteroids and other immunosuppressants for the treatment of immune-mediated adverse events. This challenge raises the question of whether the combination, if proven successful in this pivotal trial, could enter practice as a new standard in lieu of a VEGF kinase inhibitor.

Other checkpoint inhibitor combinations, including CTLA4-directed tremelimumab plus the PD-1 inhibitor Medi4736 (NCT02261220) or the anti-KIR–directed antibody lirilumab plus nivolumab (NCT01714739), are much earlier in their development for RCC. Potential synergism with cytokine therapy is being explored in an RCC expansion cohort of a phase I study combining nivolumab with recombinant IL-21 (NCT01629758).

Combining Checkpoint Inhibitors with Approved Targeted Agents

Beyond its principal role as a regulator of angiogenesis, VEGF has various immunomodulatory effects. Accordingly, VEGF tyrosine kinase inhibitors (TKIs) as well as the VEGF-A directed monoclonal antibody bevacizumab have demonstrated immune stimulatory effects across various tumor models (reviewed by Vanneman et al[19]), lending support to combining checkpoint inhibitors with approved targeted therapies. High response rates for combinations of VEGF TKI therapy with CTLA4 inhibition[20] as well as with PD-1 blockade[21] suggest that such synergism in fact exists. At the same time, these trials reported a notable increase in treatment-induced organ dysfunction. The combination of

nivolumab and standard-dose sunitinib, for instance, demonstrated encouraging antitumor activity, with an ORR of 52% across 33 patients, but grade 3 to 4 treatment-related adverse events were recorded in greater than 70% of patients.[21] Such findings make this combination hardly appear suitable for further development on a larger scale. With the suggestion of synergism, however, and in consideration of the notion that immunotherapy may extend the duration of disease control, the field should not prematurely abandon combinations of TKI and checkpoint inhibition. For further development, however, we may need to explore alternate treatment schedules, such as lower dosing levels, sequenced introduction of agents, or alternating dosing schedules. Safety data from other TKI/PD-1 combination trials is awaited, including the two combination trials pairing the PD-1–directed monoclonal antibody pembrolizumab plus pazopanib (NCT02014636) or axitinib (NCT02133742).

Similar to prior experiences combining VEGF-targeted therapy with other agents, bevacizumab seems to pair with checkpoint inhibition without notable increases in toxicity. Data from a phase I study combining bevacizumab and the monoclonal PD-L1–directed antibody MPDL3280 suggested a favorable safety profile, with less than 5% grade 3 to 4 adverse events and four of 10 patients achieving a partial response; nine of 10 patients remained on study at the time of the report.[22] This result prompted a large, randomized, phase II study (NCT01984242) that is presently enrolling untreated patients with 1:1:1 random assignment among standard-dose sunitinib, MPDL3280 monotherapy, and the combination of MPDL3280 plus bevacizumab. Thus, its favorable tolerance when used as a partner with other agents may bring attention to bevacizumab, an agent previously approved in the first-line setting but currently underutilized in that setting.

Vaccine Studies

A number of vaccination strategies, including autologous, multipeptide, and antigen-directed vaccines, are being tested in metastatic RCC.[23] Although it is unlikely that these could replace the current standard of targeted therapy in treatment-naive patients, immunomodulatory effects argue in favor of pairing vaccines with approved targeted therapies. In the phase III ADAPT trial (NCT1582672) patients undergoing cytoreductive nephrectomy were randomly assigned to standard targeted therapy plus autologous vaccination with AGS-003 or to standard therapy alone. This trial is based on encouraging data from a previous open-label, phase II study of sunitinib plus AGS-003 that reported a median PFS of 11.2 months and a median OS of 30.2 months.[23] Another phase III study (NCT01265901) is comparing standard sunitinib to vaccination with sunitinib plus IMA901, a multipeptide vaccine of nine tumor-associated peptides administered after a single dose of cyclophosphamide. Both studies have OS as a primary endpoint, because successful vaccination should have a longer-lasting immunomodulatory anticancer effect. The substantial efforts to bring checkpoint inhibitors into routine practice now raise questions for the further develop-

ment of vaccination strategies: Will these immunotherapies compete with one another in the space of metastatic RCC, or should the two approaches be investigated for synergy?

METASTASECTOMY IN ADVANCED RCC

On the basis of epidemiological estimates, up to 30,000 patients a year are diagnosed with synchronous or metachronous metastatic RCC in the European Union alone.[24] Figures for the United States are comparable.[25] There is a preference for pulmonary (45.2%), followed by skeletal (29.5%), lymph node (21.8%), liver (20.3%), and brain (8.1) % metastases.[26] Other locations of metastasis have been described at lower frequencies. Because of the extent of disease, most patients with metastatic RCC are candidates for systemic therapy rather than metastasectomy. With current targeted treatments, a cure remains elusive, and the median OS may reach 40 months in select patients with sequential therapy.[27] However, in those patients who have solitary or oligometastasis, surgical resection of all lesions when technically feasible provides the only potentially curative treatment, aside from the occasional durable responses achieved with high-dose IL-2. Surgical resection is the preferred approach for metastasectomy, but stereotactic radiosurgery (SRS) or body radiotherapy (SBRT) may be noninvasive alternatives.[28] Unlike surgical metastasectomy, SRS, SBRT, or ablative techniques have been preferred for brain, bone, and liver metastases.[29] These focal therapies are being expanded to multiple anatomic regions, but thermal ablation has been applied only in small series.

Case Selection for Metastasectomy

No reliable data exist that identify a percentage of patients with metastatic RCC who are candidates and eligible for complete surgical metastasectomy or local therapy. According to a population-based analysis, up to 65% of patients with metastatic RCC have a single anatomic site of metastasis, but most of these metastases are either multiples at that site or not resectable.[26] Potentially, only 25% of patients with metachronous metastases are suitable for metastasectomy.[30,31] For patients with synchronous metastasis, the proportion may be lower than 10%.[32] Patient selection for metastasectomy is challenging because of the heterogeneous biology of metastatic RCC and an absence of randomized, controlled trials in this setting. In addition, most retrospective studies reported results before the introduction of targeted therapy. The clinical course of metastatic RCC is unpredictable. Metastasis may present at diagnosis or within a year after nephrectomy with rapid disease progression, whereas disease-free intervals of more than 20 years followed by slow metastatic growth have been reported. In a few cases, spontaneous regression of metastases has been documented.[33,34]

The Renal Cancer Guideline Panel of the European Association of Urology performed a systematic review to address the questions of whether local therapy for RCC metastases is beneficial, and, if so, what the best therapeutic approaches are.[35] In accordance with Cochrane Review methodology and PRISMA guidelines, including all types of comparative studies on local treatment of RCC metastases in any organ, 2,235 studies were identified. However, only 16 small, retrospective, comparative studies reporting on a total of 2,350 patients were eligible for inclusion. The systematic review revealed a benefit for complete metastasectomy compared with either incomplete or no metastasectomy for metastases to various organs in terms of survival and symptom control, such as pain relief in bone metastases. There may be an additional role in delaying the start of targeted therapy and its associated adverse events. However, there were extensive risks of bias across all studies, which resulted in a significant risk of confounding. Because of the relatively poor quality of the studies, the evidence retrieved was associated with large uncertainty, and no general recommendations were made. Retrospective series are biased by comparing patients who had solitary and oligometastatic disease and a prolonged metachronous interval with those who did not undergo resection because of extensive metastatic burden, rapid disease progression, and reduced performance status. The most important determinant of outcome, therefore, may be the biologic behavior of the tumor.[36] In one series, a high nuclear tumor grade was the only adverse factor for survival.[37] In a metastasectomy-specific prognostic model, primary tumor T stage greater than or equal to 3 , primary tumor grade greater than or equal to 3, presence of nonpulmonary metastases, a disease-free interval of 12 months or fewer, and multiorgan metastases were independent pretreatment prognostic factors for survival after metastasectomy in a multivariable analysis.[38] In contrast to the commonly used Memorial Sloan Kettering Cancer Center (MSKCC) and International Metastatic Renal Cancer Database Consortium (IMDC) prognostic models, which estimate survival in metastatic RCC on the basis of five to six clinical factors, the results have not been externally validated.

Identification of patients who may benefit from metastasectomy is important, because surgical resection, including other forms of local therapy alone or in combination with targeted agents, may result in superior outcome compared with systemic therapy alone. The decision to resect metastases depends on a number of clinical factors, such as the tumor-node-metastasis staging system classification, performance status, prognostic risk factors, the length of the disease-free interval, synchronous or metachronous metastasis, the burden of metastatic disease, and the number and location of sites involved.[39] Since then, multiple retrospective series have been published that support the use of these favorable factors (Sidebar).[40-42] In particular, complete metastasectomy is a favorable prognostic variable according to data from Europe, the United States, and Japan.[43,44] Metastasectomy is associated with survival and clinical benefit across the various MSKCC risk groups.[31,45] In a retrospective analysis of 129 patients who developed metachronous metastases from RCC, metastasectomy improved 5-year survival from 36% to 71% in favorable-risk patients. For intermediate-risk patients, the 5-year survival was 38% after metastasectomy ver-

sus 0% in the same risk group without metastasectomy or with poor prognosis. Even after adjusting for risk groups in a multivariate analysis, patients without metastasectomy had a 2.7-fold increased risk of death. Previously, the same institution reported on 118 patients who had a median survival of 21 months from the time of recurrence.[31] OS was strongly associated with risk-group category (p < 0.0001). The median OS times for low-, intermediate-, and high-risk groups were 76, 25, and 6 months, respectively, and the 2-year survival rates were 88% (95% CI, 77% to 99%), 51% (95% CI, 37% to 65%), and 11% (95% CI, 0% to 24%), respectively, which suggest that only favorable- or intermediate-risk patients are candidates for metastasectomy. After the introduction of targeted therapy, the MSKCC risk model has been largely superseded by the IMDC risk model but remains a valid tool among other similar risk scores to identify potential candidates for metastasectomy.[46,47] Though the factors related to prognosis seem to be generally applicable to metastasectomy at any site, some sites may demand specific management strategies, especially when solitary metastasis or oligometastasis is present.

Metastasectomy by Anatomic Site

The lungs are the most frequently affected site, with a prevalence rate of 74% in autopsy studies.[48] Pulmonary metastasectomy is associated with longer survival than that of other sites, even when multiple lung lesions are resected. The best outcome is reported for patients who have completely resected solitary metastases after a long disease-free interval. Complete resection of up to but not exceeding seven lung metastases is associated with a 5-year survival rate of 37% to 54%.[30,49-52] Because of the high frequency of lung metastases, there is a wealth of retrospective, nonrandomized studies on pulmonary metastasectomy that suggest that unilateral lung involvement, absence of lymph node metastases, and smaller size are additional site-specific favorable factors. Complete resection, size greater than 3 cm, positive node status of the primary tumor, synchronous metastases, pleural invasion, and mediastinal lymph node metastases were independent prognostic factors on multivariate anal-

ysis identified in a lung-specific prognostic score developed from 200 patients with pulmonary metastases.[53] Three risk groups were discriminated with median OS times of 90, 31, and 14 months for low-, intermediate-, and high-risk groups, respectively. This score is not yet externally validated.

Resection of bone metastasis is mainly performed for palliation but may result in 5-year survival rates of 75%, particularly in metachronous and appendicular solitary bone lesions.[54] For symptomatic bone metastases, surgery is superior to radiotherapy. A randomized, prospective trial in patients with bone metastasis from various malignancies, which included a minority of RCC, revealed that direct decompressive surgery plus postoperative radiotherapy was superior to treatment with radiotherapy alone for patients with spinal cord compression caused by metastatic cancer.[55] The best approach for asymptomatic solitary bone lesions is unclear. If surgery is chosen, wide excision with fixation or reconstruction is preferable. For brain metastases, SRS has largely replaced surgery as local treatment. However, surgery may be preferable in lesions greater than 2 to 3 cm, with rapid onset of symptoms, and in lesions with a midline shift. Selection factors in patients for local therapy of brain metastases regardless of the primary tumor site include performance status, extracranial tumor load, and the course of disease, as summarized in the Radiation Therapy Oncology Group (RTOG) recursive partition analysis (RPA).[56] SRS yields a median OS of 24 months in patients with RTOG-RPA prognostic class I. Whole-brain radiotherapy is only adequate for patients who have a poor performance status.[57-59]

For most other metastatic sites, detailed selection criteria are not available, and indication for resection should follow the factors associated with a favorable outcome (Sidebar). Hepatic metastasis is associated with poor prognosis. Nevertheless, after complete resection for solitary lesions, 5-year survival rates of 62% have been reported.[60] Liver metastasectomy may cause significant morbidity and mortality, and it is unclear if surgery is superior to ablative percutaneous techniques. Synchronous solitary adrenal metastases are usually resected at the time of nephrectomy.[61] Management of isolated metachronous ipsi- and contralateral adrenal lesions is often reported in series of local recurrences. Survival of up to 70 months has been reported after metastasectomy after a long disease-free interval.[62] Though not regarded as a distant metastatic site in the tumor-node-metastasis staging system classification, lymph node metastases are frequent and associated with a poor outcome, similar to systemic disease.[63,64] Synchronous regional lymph node metastases often are resected at nephrectomy. Isolated lymph node metastasis without further systemic disease is rare,[65,66] but resection may be curative. Resection of metachronous isolated lymphonodular metastases often is reported in series on local recurrences.[67] Complete metastasectomy of solitary lesions in the pancreas, thyroid, and other less frequently involved sites results in 5-year survival rates comparable to those observed

after pulmonary metastasectomy.[68] Remarkably, repeat complete metastasectomy and complete resection of multiple metastatic sites are associated with long-term survival and a 50% decrease in the risk of death.[36] Multiple case reports and series on the integration of targeted therapy with surgery report neoadjuvant targeted therapy to downsize lesions or select candidates for complete resection.[69] However, the approach is experimental and not supported by prospective studies. Ultimately, to derive a higher quality of evidence regarding metastasectomy and other local treatment options in RCC, larger and prospective, randomized studies need to be performed.

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Relationships are considered self-held and compensated unless otherwise noted. Relationships marked "L" indicate leadership positions. Relationships marked "I" are those held by an immediate family member; those marked "B" are held by the author and an immediate family member. Institutional relationships are marked "Inst." Relationships marked "U" are uncompensated.

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GENITOURINARY CANCER

Controversies in the Management of Germ Cell Tumors

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The Role of Surveillance versus Adjuvant Treatment in Stage I Germ Cell Tumors: Outcomes and Challenges

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OVERVIEW

Germ cell cancers of the testis arise in young adults, and, if identified in stage I, have an excellent prognosis. Thus, we should minimize management-related toxicities. Surveillance (observation) following orchiectomy can avoid further treatment; however, patients who experience relapse receive more treatment than what would have been used during initial adjuvant therapy. For the individual patient, it is important to be aware of their particular risk of relapse, the treatment they would receive for the treatment of relapse and the alternative adjuvant approaches. For seminoma, the risk of relapse during surveillance is 15% to 20%; the size of the primary tumor and the presence of rete testis invasion are prognostic factors. Most relapses occur within 3 years; however, approximately 10% occur more than 5 years after orchiectomy. The alternative adjuvant strategies are either one cycle of carboplatin or radiotherapy (RT), which reduce recurrence risk to less than 5%. The cure rate is around 99%, regardless of which management option is implemented. For stage I nonseminoma, the risk of relapse during surveillance in unselected series is 26% to 30%. Lymphovascular invasion and the amount of embryonal carcinoma are risk factors. Most relapses occur within the first year after orchiectomy, and relapse after 3 years is rare. Ninety percent of relapse patterns are classified as ''good prognosis,'' and cure rates are 99%. The alternatives to surveillance include adjuvant strategies such as one cycle of adjuvant bleomycin/etoposide/cisplatin (BEP) chemotherapy; however, evidence is emerging that a single cycle is effective. There is controversy whether to offer surveillance for all patients or to offer adjuvant chemotherapy to select patients.

Germ cell cancers of the testis are defined as stage I when radiologic investigations show no evidence of metastasis. These generally comprise of CT scans of the thorax and abdomen, although the pelvis should also be included in patients with previous inguinal or scrotal surgery. Serum tumor markers elevated prior to orchiectomy should fall with an appropriate half-life (less than 5 days for alpha-fetoprotein and less than 2 days for human chorionic gonadotropin) after resection of the primary tumor. Men with normal radiology but persisting elevated blood tumor markers are regarded as having metastases and will not be considered further in this manuscript. Despite an increase in the sensitivity of radiologic staging tests, there appears to be an increase over recent decades in the proportion of patients with germ cell cancer in stage I,[1] with approximately 80% of seminomas and 60% of nonseminomas presenting in this stage.

A number of management policies have been followed postorchiectomy, and all are associated now with very high cure rates (around 99%). The shared aim of these policies is to address patients in stage I who actually have subclinical metastasis. These policies include surveillance, adjuvant chemotherapy, retroperitoneal lymph node dissection (RPLND), and RT.

SURVEILLANCE

This management policy involves regular monitoring of patients postorchiectomy to detect any development of clinically overt metastases at a stage in which the disease would still be highly curable. Initially, there was anxiety about allowing subclinical disease to progress, and consequently, surveillance was rather intensive. There are few prospective studies, but a Medical Research Council trial that randomly assigned 414 patients who were undergoing surveillance for stage I nonseminomas to receive five scans at months 3, 6, 9, 12, and 24, or two scans at months 3 and 12 reported similar outcomes.[2] The Royal Marsden schedule for the surveillance of patients with nonseminoma involves monthly tumor markers and chest radiographs for the first year, chest radiographs every 3 months for the second year, and chest radiographs every 4 months in the third year, as well as CT scans of the abdomen at 3, 12, and 24 months. However, a number of guidelines recommend fewer assessments without clear detriment. Similarly, there are few prospective seminoma studies; an ongoing U.K. trial is comparing CT scan schedules and MRI versus CT imaging. The Royal Marsden schedule has clinic assessments every 3 months in the first and

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second years, assessments every 4 months in the third year, and assessments every 6 months until the end of year 5, and thereafter annually up to 10 years. CT scans of the abdomen are conducted every 6 months for 2 years, then annually for an additional 3 years.[3]

In a systematic review of larger case series of nonseminoma published between 1986 and 2004, relapse rates during surveillance was 26% to 30%, and the most commonly agreed adverse prognostic factor was lymphovascular invasion (LVI) in the primary tumor.[4] A recent retrospective report[5] on surveillance outcomes based on more than 1,000 patients found that only 19% relapsed; this reduction may be a result of more sensitive staging or the practice of offering adjuvant chemotherapy to patients at higher risk. Only 16% of patients had LVI-positive disease.[5] The median time to relapse was 6 months, and the relapse risk was 44% in patients with LVI compared with 14% in patients without LVI. Out of 214 patients whose disease relapsed, 192 were prognostically classified as good risk, 16 were intermediate risk, and six were poor risk. At the time of reporting, there had been only five disease- or treatment-related deaths and an additional two patients were alive with disease.

Surveillance poses different challenges in patients with stage I seminoma because tumor markers are not necessarily helpful and the disease has a slower natural history requiring a longer period of observation. In addition, seminoma has a more predictable pattern of metastasis, which initially occurs in the retroperitoneal nodes. Approximately 15% to 20% of patients with seminoma will experience relapse during surveillance.[4] There has been some controversy over the prognostic risk model, first proposed by Warde et al[6] based on a retrospective review of 638 patients from Canada and Europe. This prognostic model suggested that the combination

of primary tumor diameter greater than 4 cm and invasion of the rete testis conferred a relapse risk of 31%, whereas only one of these factors conferred a risk of 16%, and an absence of both factors conferred a risk of 12%. Although the model has not been validated, the same risk factors were reported in the Swedish and Norwegian Testicular Cancer Group (SWENOTECA) community-based studies[7] and in the Spanish Germ Cell Group trials.[8] A retrospective study of surveillance in 1,344 patients with stage I seminoma reported that 173 patients experienced relapse and all but two patients were classified as good risk upon relapse, with most patients (87%) diagnosed by abdominal CT imaging.[5] Only one patient died as a result of the disease or treatment.

ADJUVANT CHEMOTHERAPY

The rationale for considering adjuvant chemotherapy following orchiectomy is based on the avoidance of the risk of toxicities that may occur during a full treatment of relapsed disease, as well as the disappointment and natural anxiety experienced when relapse occurs. For nonseminoma, initial studies suggested a benefit of two cycles of BEP[9]; however, more recently there have been persuasive reports suggesting a benefit with a single cycle. A German Testicular Group trial randomly assigned patients to undergo RPLND and one cycle of BEP.[10] Of 191 patients treated with BEP, the relapse risk was only 0.5%. Similarly, a community protocol by the SWENOTECA group that included 517 patients who received one cycle of adjuvant BEP reported relapse rates of 1.6% for patients with LVI-negative and 3.2% for patients with LVI-positive tumors.[7] An ongoing U.K. prospective trial (The 111 Trial) that will evaluate the outcomes of one cycle of BEP completed recruitment of 246 high risk patients in July 2014 and results are expected to be reported soon.

In patients with seminoma, the decision to offer adjuvant chemotherapy has been based on a low toxicity approach using single agent carboplatin. A large, prospective, randomized, controlled trial compared traditional adjuvant RT to one cycle of carboplatin at a dose intended to achieve an area under the curve (AUC) of 7 mg × mins/mL.[11] Of 573 men randomly assigned to receive carboplatin, the relapse rate was 4%, which was similar to RT. This result for carboplatin was similar to the SWENOTECA community study conducted in 188 patients with seminoma, in whom the relapse rate was 4% after a median follow-up of 3.4 years.[12] In the Spanish Testicular Germ Cell Group trials, the relapse rate after two cycles of carboplatin was 3.2%.[8]

RETROPERITONEAL LYMPH NODE DISSECTION

The rationale of this approach was to provide more accurate staging of retroperitoneal nodes and to reduce relapse risk in those with subclinical metastases confined to those nodes. However, the surgery is not trivial and is only proficiently performed in specialized centers. The German Testicular

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KEY POINTS

- Men with stage I testicular germ cell cancer have an excellent prognosis with reported cure rates of 99%, regardless of the management option chosen postorchiectomy.
- In unselected patients with nonseminoma, there is a relapse risk of 25% to 30% during surveillance, and the most widely recognized risk factor is lymphovascular invasion.
- In unselected patients with seminoma, there is a relapse risk of 15% to 20% during surveillance, and the most widely recognized risk factors are tumor diameter and rete testis invasion.
- Radiotherapy has the relative disadvantage that it is carcinogenic.
- The primary management options following orchiectomy are surveillance or adjuvant chemotherapy, and patient preferences should be respected. Risk-adapted selection for adjuvant chemotherapy markedly reduces the risk of recurrence during the remainder of the time spent in surveillance.

Group multicenter trial discussed previously had 15 recurrences in 191 patients who were randomly assigned to undergo RPLND (92% of patients achieved 2 years of relapse-free survival), of which seven patients had disease involvement in the retroperitoneal nodes.[10] Single, specialized center experience suggests that careful staging and selection for adjuvant chemotherapy can increase the proportion of patients with stage II found to have low volume node disease and achieve a very low recurrence.[13]

RADIOTHERAPY

This has been a standard adjuvant approach in patients with stage I seminoma, traditionally to a field including both para-aortic and ipsilateral pelvic lymph nodes. Many series reported recurrence risk of less than 5%. More recently, prospective, randomized trials have shown that reducing the field to just the para-aortic region[14] and reducing the dose to only 20 Gy[15] did not reduce efficacy. The disadvantage of RT is that it is carcinogenic. For example, a multicenter U.K. and Norwegian study of 2,692 patients with stage I seminoma demonstrated a cancer Standardized Incidence Ratio of 1.53 when second testicular cancers were excluded,[16] with increased risk mainly affecting cancers of abdominal organs. This risk has led to the option of adjuvant RT for patients with stage I seminoma being abandoned or reduced considerably in some communities.[17-19]

DISCUSSION

In most oncology centers, the primary management options in 2015 for patients who have undergone an orchiectomy for stage I testicular cancer are surveillance or adjuvant chemotherapy. There are advocates in favor of surveillance for almost all patients with stage I testicular cancer on the grounds that it is safe in terms of ultimate cure rate and that it confines the potential toxicities of treatment to the minority of patients whose disease has already formed subclinical metastases.[20] The arguments for adjuvant chemotherapy suggest that the limited total drug doses in one treatment cycle are safer for patients than the drug doses in a full treatment for metastatic relapse. In addition, adjuvant chemotherapy has a particular indication in patients with high risk features, in patients who are unlikely to adhere to surveillance, and in patients with comorbidities that might compromise a full course of treatment for metastases. This leads to a so-called risk-adapted strategy, with surveillance for patients at low risk and adjuvant chemotherapy for patients at a high risk of developing metastasis, as promoted particularly in the Spanish Germ Cell Cancer Group trials.[21] There is a strong argument to involve the individual patient in the discussion of both approaches.[22]

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Germ Cell Tumors: Looking to the Future

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OVERVIEW

Our knowledge about the management of men with germ cell tumors (GCTs) and its tumor biology continues to evolve. Vascular disease, metabolic syndrome, second malignant neoplasms, and hypogonadism occur after treatment for GCTs and the latency pattern resembles that seen in patients treated for Hodgkin lymphoma. Patients receiving treatment for GCTs should be informed not only of the near-term toxicity (experienced during or shortly after administration), but also the delayed and late effects of chemotherapy and the need for lifelong surveillance for all late outcomes, including late relapse. Recent data suggest that the treatment outcome of patients with intermediate-risk, poor-risk, and relapsed GCTs can be improved through multicenter trials that include the general oncology community. Finally, GCTs are a malignancy of primordial germ cells. Programmed differentiation is clinically evident in vivo and probably related to chemotherapy resistance. This biology has much clinical relevance, some of which is already in use.

In 2015, more than 90% of men with newly diagnosed GCTs will be cured. The chemotherapy backbone of etoposide/cisplatin (EP) with or without bleomycin (BEP) cures patients with even far advanced newly diagnosed metastatic disease. A sizable proportion of patients who relapse or progress after initial chemotherapy are cured with standard and high-dose regimens.[1] Since chemotherapy cures nearly all patients with low-volume disease, surveillance has become a standard of care for patients with clinical stage (CS) I seminoma and CS I-A nonseminomatous GCT (NSGCT), few of whom relapse after orchiectomy. Adjuvant chemotherapy with one or two chemotherapy cycles has been adopted by some for CS I-B disease and is often recommended for patients who have pathologic stage IIB disease at primary retroperitoneal lymph node dissection.[1,2]

However, physicians and patients should not be misled. Attention to detail may be more important in the management of patients with GCTs than in any other curable malignancy since a large proportion of patients is observed without treatment after orchiectomy and easily lost to follow-up. The number of survivors is increasing, with close to 250,000 survivors of GCTs comprising approximately 4% of all male cancer survivors, more than lung cancer.[3] Despite the low death rate, the number of lost life years is greater for patients with GCTs than for any other cancer in adults.[4] Complacency, fostered by the high cure rate, obscures the effect of rare fatal events resulting from improper diagnosis, loss to follow-up, late chemotherapy side effects, the need for improved therapy for intermediate-, poor-risk, or relapsed disease, and the poor understanding of GCT bi-

ology. What should oncologists be looking for in the next 10 years?

MANAGEMENT OF SURVIVORS

"An individual is considered a cancer survivor from the time of diagnosis to the balance of his or her life" (Office of Cancer Survivorship) and survivorship deals "…with the full spectrum of survivorship issues related to living with, through, and beyond the cancer diagnosis" (National Coalition of Cancer Survivors).[5,6] Hence, men with GCT should be followed long after being rendered free of disease. Indeed, the oncologist may be the only physician that these young patients have. Although persistent peripheral neuropathy, ototoxicity, and hypogonadism are observed, cardiovascular disease and second malignant neoplasms are the most important late effects since they can be life threatening.

Cardiovascular Disease

Both acute and late toxicities exist for men with GCTs. Venous and arterial vascular events may occur during cisplatin-based chemotherapy (and rarely carboplatin), including myocardial infarction, stroke, peripheral arterial thrombosis, and pulmonary emboli.[7,8,9] Delayed vascular toxicity presenting as Raynaud's phenomenon occurs in 6% to 7% of patients receiving bleomycin as part of chemotherapy for GCT.[10,11,12] Cardiac and rare cerebrovascular morbidity and mortality may occur 10 to 20 years (or more) after the completion of chemotherapy.[13,14,15] Although the mechanism is not understood, insulin resistance, increased abdominal visceral fat, and hyperlipidemia may appear shortly after che-

motherapy, and metabolic syndrome with or without hypogonadism, which is associated with increased cardiovascular morbidity and mortality, is more frequent in men who receive GCT chemotherapy.[16,17,18]

To mitigate these risks, patients should be monitored after chemotherapy for the onset of hypertension, obesity, hyperlipidemia, and hypogonadism, with intervention at the earliest opportunity.[19] Smoking cessation and weight reduction are key to cardiovascular protection. If the oncologist will not be following the patient long-term, then a primary care physician should oversee general health maintenance.

Second Malignant Neoplasms

Patients with GCTs have an increased risk for second non-GCT neoplasms after both radiation therapy (RT) and chemotherapy,[20,21] but not after surgery alone.[21] RT increases the incidence of several intra-abdominal neoplasms, including colon, pancreas, and stomach cancer.[20,22] Although surveillance has largely replaced RT for CS I seminoma, RT exposure is prevalent among survivors of GCT since most received RT for seminoma before 2005, the year of the Travis report.[20] Early screening colonoscopy should be considered, as is recommended for survivors of childhood malignancy.[23] The lower bound of chemotherapy dose associated with the risk for second non-GCT malignant neoplasms is unknown. Therefore, the use of chemotherapy in the adjuvant setting, particularly CS I-B NSGCT, has unknown long-term risks. However, even the lowest doses of etoposide are associated with an increased risk for leukemia,[24] suggesting that the long-term effects of adjuvant administration, merits consideration. Last, men with GCT are disproportionately likely to have multiple atypical nevi and melanoma.[20,25] Although melanoma is not caused by treatment, dermatologic referral of patients with GCT and pigmented nevi should also be considered.

KEY POINTS

- Late effects of cisplatin-based chemotherapy for GCT are known and should be discussed with all patients who require it.
- In good-risk disease, new guidelines list four cycles of etoposide/cisplatin and three cycles of bleomycin/etoposide/cisplatin as options for clinical stage IIA and IIB seminoma.
- Treatment outcome in patients with intermediate-, poor-risk, and relapsed disease may improve because of recent and ongoing trials.
- Most data indicate that few GCTs display driver mutations and a better knowledge of tumor biology is needed to identify potential therapeutic targets.
- Progress will require a national and international trial effort including participation by community oncologists to accrue adequate patients and tumor sample for studies.

SYSTEMIC THERAPY FOR METASTATIC DISEASE
Good Risk

Since 90% to 95% of patients with good-risk disease are cured, improvements on three cycles of BEP (BEPx3) and four cycles of EP (EPx4) are unlikely. The lower bound of efficacy is known and carboplatin is inferior to cisplatin in both relapse rate and cure rate.[1] The management of CS IIA and IIB metastatic seminoma with chemotherapy rather than RT is evolving. Recent studies report no relapses among 20 patients with CS IIA disease and 22 patients with CS IIB disease.[26,27] Since RT leads to an increased incidence of intra-abdominal malignancy, and RT followed by chemotherapy leads to an even greater likelihood of both late cardiovascular and second cancer events than either modality alone,[28] primary chemotherapy has been added to the National Comprehensive Cancer Network guidelines for these two groups.[29]

Intermediate and Poor Risk

Four trials suggest that better outcomes can be achieved in patients with intermediate-risk and poor-risk disease, who have cure rates of approximately 75% and 50%, respectively.

In the first trial, paclitaxel added to BEP in intermediate-risk disease led to a significant 12% improvement (p = 0.03) in 3-year progression-free survival when ineligible patients were excluded, but a nonsignificant improvement in the intent-to-treat analysis.[30]

A second randomized trial comparing standard-dose BEP with a dose intense regimen with stem cell support resulted in a 16% improvement in failure-free survival, which was not significant (p = 0.057).[31] Both trials were closed early because of slow accrual, partly because of separation of intermediate-risk and poor-risk groups into different studies, leading to nonsignificant results despite trends suggesting improved survival.

A third randomized trial of standard BEPx4 compared with a complex BEP-based regimen with paclitaxel, oxaliplatin, and ifosfamide in patients with poor-risk disease and an unfavorable tumor marker decline showed an improvement in 3-year progression-free survival from 48% to 59% (p = 0.05), but with more grade 3 to 4 toxicity.[32]

Finally, a phase II trial of four cycles of paclitaxel/ifosfamide/cisplatin (TIPx4) demonstrated a 95% 3-year overall survival and 79% 3-year progression-free survival.[33]

Together, these results suggest that the outcome of intermediate- and poor-risk disease can be improved. Since three of these trials incorporated paclitaxel, a direct comparison of TIPx4 to BEPx4 is now open at several institutions (NCT01873326). A worse outcome when the half-life of either alpha-fetoprotein (AFP) or human chorionic gonadotropin (HCG) is prolonged was also demonstrated in an intergroup study in which an improvement in 1-year survival was observed in patients with slow marker decline from 34% for BEPx4 to 61% for BEPx2 followed by two cycles of high-dose chemotherapy.[34] Thus, a randomized trial testing a new regimen in patients selected for unfavorable marker decline is reasonable. In both cases, the trials should be multicenter/multinational and include and stratify for intermediate- and poor-risk disease.

Salvage Therapy

Patients who have relapsed after complete remission or responded but failed to achieve a complete remission (incomplete response) have potentially curable disease.[35-38] Some groups favor standard-dose therapy for relapse after a complete response and high-dose therapy restricted to incomplete responders, whereas others favor the administration of high-dose chemotherapy to all patients.[36,37] Disagreement exists as to the proper management of patients with mediastinal and nontesticular NSGCT (e.g., ovarian, pineal).[36,37] Other investigators question the benefit of high-dose therapy.[38] A randomized trial in Europe and the United States stratified for prognostic subgroups will test the hypothesis that high-dose chemotherapy is better than standard-dose chemotherapy as initial salvage treatment for patients with relapsed or progressive GCT.[39,40]

GCT BIOLOGY AND ITS CLINICAL IMPLICATIONS

GCT biology is clinically relevant. One of the provocative questions raised by the National Cancer Institute is the study of "what molecular properties make some cancers curable with conventional chemotherapy."[41] The differential chemotherapy sensitivity of seminoma and NSGCT is reflected in the International Germ Cell Cancer Consensus Group (IGCCCG) classification.[42] In metastatic seminoma, only nonpulmonary visceral metastases qualify as intermediate risk; poor-risk seminoma does not exist. In contrast, blood marker levels, sites of nonpulmonary metastases, and mediastinal primary site establish the good-, intermediate-, and poor-risk strata in NSGCT, on which the choice of treatment depends. Adherence to the IGCCCG classification is central to assuring neither overtreatment nor undertreatment. Although both seminoma and NSGCT are highly curable, the biology responsible for the differential chemotherapy sensitivity of seminoma/NSGCT histology, marker production, and mediastinal primary site is unknown.

Derivation from Primordial Germ Cells

GCTs are derived from primordial germ cells (PGCs). The fetal migration of PGCs from the genital ridge to the testis is regulated by the interaction of CD117 (the c-kit receptor) expressed by PGC and its ligand, stem cell factor (kit ligand), and is essential to spermatogenesis in the postpubertal male.[43] The expression of CD117 disappears during early meiosis. Seminoma are closest to the unipotent germ cells and expresses CD117 and embryonal carcinoma acquires pluripotency and does not express CD117. *NANOG, POU5F1,* and *SOX2* are genes that encode three key master regulator transcription factors (Nanog, Oct4, and Sox2) required for the maintenance of pluripotency in murine and human embryonic stem cells (ESC).[44,45] Both seminoma and NSGCT express Nanog and Oct4; only embryonal carcinoma expresses all three. Downregulation of these genes' expression during differentiation in both embryonal carcinoma and ESC is associated with a large and complex transcription

factor network, whose dysregulated expression is probably responsible for the diverse but disorganized differentiated histologies displayed by NSGCT.[46]

These observations are useful clinically. Immunostaining for Oct4 has replaced placental alkaline phosphatase (PLAP) as the immunohistochemical marker for seminoma and embryonal carcinoma. Immunostaining for CD117 characterizes seminoma and is absent in embryonal carcinoma. CD30, generally regarded as a marker of anaplastic large cell lymphoma and Reed-Sternberg cells, is also expressed by embryonal carcinoma but not seminoma.[47] Subsequent work indicated that CD30 is a survival factor for transformed human pluripotent human ESC. Finally, embryonal carcinoma expresses keratins and seminoma does not, indicating its more differentiated state. A combination of Oct4, CD117, CD30, and keratins is now part of the standard diagnostic immunohistochemical panel when a diagnosis of GCT is under consideration.[48,49]

Differentiation and Resistance

Treatment resistance in GCTs is likely related to genetic events leading to differentiation.[50] Clinical observations support this hypothesis. Seminoma is more sensitive than NSGCT.[42] Teratoma, usually displaying benign-appearing mature and immature cell types, is insensitive to chemotherapy and must be surgically excised. Yolk sac and trophoblastic differentiation, reflected by secretion of AFP and HCG, respectively, is associated with worsening prognosis as serum levels become higher.[42] Late relapse of NSGCT often displays yolk sac differentiation and is associated with a relatively poor prognosis and reduced chemotherapy sensitivity. Finally, somatic malignant differentiation within teratoma has the prognosis of the de novo tumor arising at its natural primary site and is not sensitive to cisplatin-based GCT chemotherapy.

The secretion of AFP and HCG by embryonal carcinoma implies that the genetic machinery to manufacture these proteins may exist even if yolk sac or trophoblastic morphology is absent. Therefore, NSGCT may also express many of the intracellular proteins that represent differentiation into ectodermal, mesodermal, and endodermal lineages during normal development, sometimes with and sometimes without the characteristic morphology of teratoma.[51] A molecular signature prediction model, independent from the IGCCCG risk strata, was developed that showed that the dysregulated expression of these developmental proteins, including neuroectoderm, kidney, and other markers, was associated with a worse outcome in NSGCT.[51] This finding is consistent with clinical observations that show somatic malignant transformation of teratoma has a poor prognosis, including primitive neuroectodermal tumors (PNET), one of the more frequent forms of malignant transformation.[52,53] Replication and validation of that study on paraffin-embedded tissue are needed. Studies of gene expression within primary tumors may point to which teratoma needs resection, which will remain quiescent after chemotherapy, and why mediastinal NSGCT has such a poor prognosis. Hence, the link between pluripotency,

TABLE 1. Late Effects Spectrum of Germ Cell Tumors and Hodgkin's Lymphoma to Include in Your Treatment Discussion[28,62,63]

Disease	Modality	Event	15 Years (Approximate)	25 Years (Approximate)
Hodgkin's Lymphoma	Not stated	CVD	3%	8%
		SMN	5%	15%
GCT	RPLND	CVD + SMN	2%	8%
	RT	CVD + SMN	4% to 5%	13%
	Chemotherapy	CVD + SMN	4% to 5%	13%
	RT + chemotherapy	CVD + SMN	12%	32%

Abbreviations: CVD, cardiovascular disease; GCT, germ cell tumor; RT, radiation therapy; RPLND, retroperitoneal lymph node dissection; SMN, second malignant neoplasm.

differentiation, and drug resistance in GCT requires further study.

Genomic Change and Targeted Therapy

Although GCT displays hyperdiploidy and excess 12p copy number, most frequently as an isochromosome of 12p [i(12p)], GCT is infrequently associated with oncogene driver mutations. *BRAF* mutations were reported to be associated with a poor outcome, but a larger study showed that zero of 46 resistant tumors harbored a *BRAF* mutation.[54,55] *FGFR3* mutations were rarely detected in both sensitive and resistant tumors, whereas, *RAS, AKT1,* and *PI3KCA* mutations were observed rarely only in resistant tumors.[55] Together, these data imply that newer targeted therapies are not likely to be effective.[55] Gene amplification and *TP53* mutations have been reported in a few resistant tumors, but further study is needed to determine their relevance to prognosis and therapy.[56,57]

The expression of CD117 by seminoma and CD30 by embryonal carcinoma raises the possibility of therapy directed at these known targets. Unfortunately, imatinib was not effective in a small group of resistant tumors expressing CD117.[58] Brentuximab vedotin in embryonal carcinoma might be more promising since a complete response has been reported.[59] However, its value is likely to be minimal since most NSGCT are mixed tumors and CD30 is expressed only by embryonal carcinoma. Sunitinib and ARQ197 (a MET inhibitor) demonstrated no activity.[60,61]

Summary

Knowledge about GCTs continues to expand. Postchemotherapy vascular disease, metabolic syndrome, second malignant neoplasms, and hypogonadism occur with a latency resembling that seen in patients treated for Hodgkin lymphoma (Table 1).[62,63] Acute leukemia has been reported with the use of etoposide 500 mg/m^2 to 1,000 mg/m^2 (one to two cycles) and even a single dose of cisplatin has a measurable effect on renal function.[24,64] Although chemotherapy will cure most metastatic disease, its use should be carefully considered in adjuvant settings and patients should be informed not only of the near term effects of chemotherapy (experienced during or shortly after its administration), but also its delayed and late effects that require lifelong surveillance for late outcomes, including late relapse.[65] Clinical trials designed to improve treatment outcome in patients with intermediate-risk, poor-risk, and relapsed GCTs are feasible, but require collaboration for adequate accrual. Finally, GCT is a disease of PGCs, and differentiation is clinically evident in vivo and probably related to chemotherapy resistance. This biology has much relevance, some of which is already in clinical use. More study is needed.

Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

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Salvage Therapy in Patients with Germ Cell Tumors

Lawrence H. Einhorn, MD

OVERVIEW

Testicular cancer is the most curable metastatic solid tumor. Initial chemotherapy is evidence based with risk stratification into three prognostic categories: good, intermediate, and advanced disease. Guidelines for disease management following progression after initial cisplatin combination chemotherapy are less clear. Options include salvage surgery for patients with anatomically confined relapse, standard-dose cisplatin combination chemotherapy, or high-dose chemotherapy with carboplatin plus etoposide with peripheral blood stem cell transplantation. Proper interpretation of a presumed relapse can be complicated. Growing masses on imaging studies might reflect a growing teratoma. Persistent elevations of serum human chorionic gonadotropin (hCG) or alpha fetoprotein (AFP) are only an indication for salvage therapy if there is a definitive rise in the tumor marker. Elevated and rising serum hCG as the only evidence of recurrence can be because of cross reactivity with luteinizing hormone or usage of marijuana rather than progressive cancer. Elevated liver function tests can cause rising serum AFP.

The initiation of cisplatin combination chemotherapy 40 years ago transformed metastatic testicular cancer into a highly curable malignancy.[1] It is widely recognized to be the most curable solid tumor. Subsequent salvage strategies have allowed for cure in a substantial percentage of progressive disease following first-line cisplatin combination chemotherapy. This article will detail strategies for salvage chemotherapy, the judicious use of salvage surgery, and data from published studies.

The first curative salvage chemotherapy utilized the two-drug synergistic combination of cisplatin plus etoposide in patients in which cisplatin plus vinblastine plus bleomycin failed.[2] Our strategy at the inception of this phase II study, initiated in 1978, is still appropriate today, namely the continued use of cisplatin unless a patient's disease progressed within 4 weeks from his prior regimen (platinum refractory) and the incorporation of other active agent(s) not previously utilized. In this early study, we achieved a 25% cure rate, demonstrating the synergism of this two-drug combination. Neither single-agent cisplatin nor etoposide would be expected to have any realistic prospect for cure as second-line chemotherapy. Subsequently, etoposide replaced vinblastine as first-line chemotherapy. Subsequent standard-dose salvage regimens for patients who did not have platinum refractory disease consisted of either vinblastine plus ifosfamide plus cisplatin or paclitaxel plus ifosfamide plus cisplatin (TIP).[3-5] Today either of these standard-dose salvage chemotherapy programs are appropriate as second-line chemotherapy.

The era of successful high-dose chemotherapy with bone marrow or peripheral blood stem cell transplant began in 1986 with the introduction of carboplatin. The philosophy of autologous stem cell transplant is to utilize high doses of cytolytic agents that are active for that particular malignancy and for which major dose-limiting toxicity can be rescued by the stem cell transplant, namely myelosuppression. This has largely been a failed strategy in other solid tumors such as melanoma and breast cancer. We began studies with high-dose carboplatin and etoposide in 1986 with bone marrow transplants,[6] and subsequently with peripheral blood stem cell transplants in 1996.[7] The latter study enrolled 184 consecutive patients, of whom 116 of 184 (63%) are continuously disease free, including 22 of 49 (45%) who received treatment as third-line therapy, and 18 of 40 (45%) who were deemed to have platinum refractory disease.[7] This study demonstrated the ability of high-dose platinum plus etoposide to overcome drug resistance from standard doses of cisplatin and etoposide.

Memorial Sloan Kettering Cancer Center has pioneered an innovative approach with three courses of high-dose carboplatin plus etoposide (compared with the tandem transplant at Indiana University) albeit at somewhat lower doses.[8] This regimen is preceded by paclitaxel and ifosfamide (TI-CE). There are no randomized studies suggesting any specific strategy of high-dose chemotherapy is preferred. There does not appear to be optimal benefit when only one course of high-dose chemotherapy is used.[9] Likewise, there is indirect evidence that adding a third drug to carboplatin plus etoposide is not beneficial.

There also have been no randomized phase III studies suggesting or proving superiority of one form of standard-dose salvage chemotherapy. Likewise, there is no evidence-based medicine demonstrating that initial salvage chemotherapy should be high-dose versus standard-dose chemotherapy. A retrospective international analysis was performed by Lorch et al that categorized salvage chemotherapy patients into five prognostic subtypes.[10] In a retrospective analysis, the same group of

investigators compared standard-dose with high-dose chemotherapy as initial salvage chemotherapy in 1,594 patients. Seven hundred and seventy-three patients received a standard dose and 821 received high-dose chemotherapy with 2-year progression-free survival being 27.8% versus 49.6% and 5-year survival being 40.8% versus 53.2%.[11] High-dose chemotherapy is the preferred option for patients with platinum refractory disease or for patients with disease progressing after standard-dose salvage chemotherapy. However, there are no prospective randomized studies proving superiority of high-dose chemotherapy. An argument can also be made that there are no phase III trials proving the merit of standard-dose cisplatin plus ifosfamide combination chemotherapy. A randomized trial comparing TIP versus TI-CE is on the drawing board for initial salvage chemotherapy. If this trial can be completed, it would answer the question comparing these two regimens.

Testis cancer is clearly a remarkably chemosensitive and chemocurative tumor. However, it is also the most curable cancer with surgery alone as initial therapy for node-positive disease. Salvage surgery is the preferred option for initial salvage therapy if progression is anatomically confined and surgically resectable.[12]

ADDITIONAL SALVAGE THERAPIES

It is very difficult, if not impossible, to cure disease with further standard-dose platinum-based chemotherapy after high-dose chemotherapy fails. Approximately 10% of such patients will experience a 5-year disease-free survival with weekly paclitaxel plus gemcitabine, assuming they have not received prior paclitaxel therapy such as TIP.[13] Modest success has also been achieved with gemcitabine plus oxaliplatin or adding paclitaxel plus gemcitabine plus oxaliplatin.[14,15] There remains a cohort of patients in which their disease is not cured. Feldman et al evaluated 97 such patients treated with various single agents. There was only one patient partial remission and 15 patients with stable disease.[16] Daily oral etoposide is as reasonable as any approach in the management of this disease in this patient population.[17]

SPECIAL CONSIDERATIONS

A rising tumor marker (e.g., serum hCG or AFP) usually implies progressive cancer. However, marijuana, recent mononucleosis, or cross-reactivity with luteinizing hormone can cause double-digit hCG elevation. Benign liver disease can cause high AFP levels. A rising LDH should never be an indication for salvage chemotherapy. Also, a rising hCG or AFP in the absence of radiographic progression might indicate a sanctuary site relapse in the brain or a second primary in the contralateral testis. Patients with persistent elevated tumor markers after initial chemotherapy should not be considered for salvage chemotherapy unless there is a clear increase in hCG or AFP. This is especially true for patients with advanced disease presenting with serum hCG higher than 50,000 mIU/mL. Such patients will have a rapid descent in hCG after the first two courses and then have a plateau in further decline. It might take several months postchemotherapy to normalize an hCG in this patient population.[18]

Radiographic progression with normal markers might indicate a growing teratoma rather than progressive germ cell cancer.

Late relapse ($>$ 2 years postchemotherapy) occurs in 2% to 3% of patients. Disease in these patients is rarely curable with any form of salvage chemotherapy in the absence of surgery. Resection, if feasible, is the preferred option.[19]

Progressive primary mediastinal nonseminomatous germ cell tumors are particularly difficult to cure with salvage therapy.[20] Standard-dose salvage therapy will virtually always fail to produce a durable remission. Options are high-dose chemotherapy or surgical resection of a localized relapse.[8,21]

CONCLUSION

Patients with relapsing disease after being managed with cisplatin combination chemotherapy are still curable, but it is very complicated. It is recommended that such patients be seen, or at least consulted, at tertiary centers with surgical and medical oncology expertise in germ cell tumors.

KEY POINTS

- Optimal strategy for management of relapse after initial cisplatin combination chemotherapy can be complicated.
- Occasionally localized relapsed disease can be cured with salvage surgery rather than salvage chemotherapy.
- Standard-dose cisplatin-combination salvage chemotherapy incorporates active drugs not previously utilized.
- Paclitaxel plus ifosfamide plus cisplatin or vinblastine plus ifosfamide plus cisplatin are examples of standard-dose salvage chemotherapy.
- High-dose chemotherapy with carboplatin plus etoposide with peripheral blood stem cell transplant has a high cure rate with acceptable toxicity.

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GENITOURINARY CANCER

Debate on Chemotherapy and Radium 223 for the Optimal Treatment of Advanced Prostate Cancer

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Why Chemotherapy Should be Given Early for Men with Metastatic Prostate Cancer

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OVERVIEW

Metastatic hormone-sensitive prostate cancer (mHSPC) is an incurable disease, and despite a high response rate to androgen-deprivation therapy (ADT), outcomes have not significantly changed for many decades. Earlier attempts at multitargeted strategies with the addition of cytotoxic chemotherapy to ADT did not affect survival. As more effective therapies are emerging, including cytotoxic therapy for patients with metastatic castrate-resistant prostate cancer (mCRPC), there is increasing interest for testing these drugs earlier in the disease course. The premise is that agents with clinical benefit in advanced mCRPC may have a better effect if used preemptively before the development of significant resistance and to attack earlier de novo androgen resistant/independent clones. The recent results of the phase III clinical trial E3805 investigating ADT with or without docetaxel in mHSPC provide compelling support for this strategy. Docetaxel combined with ADT significantly improved overall survival from 44 to 57.6 months (p = 0.0003), particularly in patients with high-volume disease (from 32.2 to 49.2 months; p = 0.0006). Longer follow-up is needed to assess the effect on patients with low disease burden. Further studies are needed to further maximize the antitumor effect in patients with mHSPC and to investigate the effects of advancing therapy to this disease setting on the efficacy of respective agents in the castration-resistant setting.

Despite stage migration, a significant number of patients with prostate cancer develop metastasis despite curative intent primary therapy or are diagnosed with de novo metastatic disease. Until recently, the initial management of patients with newly diagnosed mHSPC has not radically changed. Since 1941 when Huggins and Hodges demonstrated the androgen dependency of prostate cancer, the mainstay of therapy has been surgical or medical castration. Clinical research has mostly focused on investigating and optimizing different strategies to deliver, potentially enhance the ADT effect, and reduce its side effects such as combining androgen receptor (AR) blockade with primary gonadal suppression, peripheral blockade only, or using intermittent versus continuous ADT. ADT with a luteinizing-hormone-releasing hormone (LHRH) agonist with or without an antiandrogen, and more recently LHRH antagonist, has almost completely replaced surgical castration as first-line treatment. Irrespective of ADT modality or schedule, patients with mHSPC treated with ADT have a median overall survival (OS) around 49 months.[1] Despite the very high initial response rates to ADT, the duration of response is limited and most patients will eventually progress to castration resistance, the deadly phenotype of the disease.

The last decade has witnessed substantial scientific progress and developments that have impacted management of metastatic castration-resistant prostate cancer (mCRPC).

This began with the key discoveries indicating that emergence of resistance to ADT is in part an adaptive process via AR-dependent and AR-independent mechanisms.[2-4]

Microtubule targeting chemotherapy, docetaxel and cabazitaxel, have demonstrated activity in advanced prostate cancer, supporting the concept that castration-resistant cells are inhibited by chemotherapy.[5-7] The effect of targeting the AR signaling in patients with advanced prostate cancer is now well established with the survival benefits demonstrated by abiraterone and enzalutamide in men with castration resistance disease irrespective of prior chemotherapy.[8-11] Drugs targeting other pathways such as sipuleucel-T (dendritic cell-based vaccine) and radium-223 (alpha-emitter and calcium mimetic) have also shown improved survival benefits in patients with mCRPC.[12-13] Despite the recent success of novel therapies, the overall effects on survival are still modest. Furthermore, the quality/quantity of responses observed in patients being treated with AR-signaling agents decrease in the context of prior treatment with another AR-signaling agent in mCRPC.[14]

Although docetaxel was the first agent approved for mCRPC, the rapid proliferation of newer non chemotherapeutics particularly oral AR targeted therapy has shifted the dynamics to delay chemotherapy. Population based studies have shown that only about a third of patients with mCRPC

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are receiving docetaxel.[15] Although speculative, one explanation may be the poor performance status of patients in the context of disease progression after receiving several lines of therapy. Anecdotal experience and recent report by Azad et al[14] on a retrospective study investigating the efficacy of enzalutamide following abiraterone in docetaxel-naïve and docetaxel-exposed patients indicated that the antitumor activity of enzalutamide following abiraterone is limited. The median duration of enzalutamide treatment was 4.1 months. Importantly, the efficacy of enzalutamide was comparable in docetaxel-naïve and docetaxel-exposed patients in terms of PSA response rates (26% vs 22%; p = 0.8), median time to radiologic/clinical progression (6.6 vs. 4.6 months; p = 0.6), and median OS (8.6 vs. 10.6 months; p = 0.2). These findings are important given the increasing evidence suggesting benefits with earlier use of docetaxel in advanced prostate cancer.

CHEMOTHERAPY IN METASTATIC HORMONE-SENSITIVE PROSTATE CANCER: SCIENTIFIC RATIONALE

Elucidating the mechanisms of prostate cancer progression to castration resistance has captivated the interest of re-searchers over several decades. Molecular adaptation of cancer cells to an androgen-deprived environment, including AR-driven pathways, activation of survival pathways bypassing AR, and clonal selection of androgen-insensitive clones, appear to be some of the major mechanisms of resistance. Molecular adaptation involves the activation of the AR through different mechanisms including AR-gene amplification, AR-overexpression or mutation, extragonadal production of androgens, ligand-independent activation by growth factors, or alteration in survival pathways bypassing AR.[2-4] In clonal selection, androgen ablation creates a host environment in which the androgen-insensitive tumor cells have a selective growth advantage over the androgen-dependent cells. The continuous proliferative growth of these androgen-independent tumor cells leads to the relapse phenomenon.[16] Isaacs and Coffey conducted the initial studies to show that progression from an androgen-sensitive to androgen-insensitive state is dependent on the initial heterogeneity of the tumor with preexisting clones of both androgen-dependent and androgen-independent cells.[16] Following castration, adult male rats bearing the androgen-sensitive Dunning R-3327-H tumor showed an initial response with decreased growth rate. However, after 60 days, androgen ablation causes selection and growth advantage of androgen-independent cells. In this model, the continuous exponential growth of the androgen-insensitive tumor cells eventually kills the host animals.[16]

The heterogeneity with regard to androgen sensitivity and the selection of resistant cells supports the need for a multi-targeted treatment approach early in the course of the disease to maximize the antitumor effect and prevent development of resistance. The use of early chemotherapy may address the phenotypically heterogeneous subpopulation of tumor cells and eliminate androgen-independent clones, allowing for a potentially improved therapeutic effect.

Traditionally, chemotherapy including docetaxel is offered to patients with mCRPC, often when symptomatic and with large disease burden. In fact, several of the recently designed trials had "delay time to chemotherapy" as a metric for "clinical success." However, delaying chemotherapy to this point may very well limit the efficacy of chemotherapy possibly because of a larger proportion of resistant cells, including chemotherapy-resistant cells within the bigger population of castration-resistant cells. The early use of cytotoxic chemotherapy may improve outcomes by attacking clones resistant to ADT before they expand or acquire more resistance or simply killing more cancer cells when they are more vulnerable.

Preclinical data by Tang et al[17] evaluated different sequences of docetaxel and androgen ablation in severe combined immunodeficient mice inoculated with the LNCaP prostate cell line. Tumor volume was at least 50% smaller in all docetaxel groups compared with castration alone. The smallest tumors at week 4 and the greatest growth delay were found in mice treated with docetaxel for 2 weeks, followed by castration. Apoptosis assays also indicated a greater degree of apoptosis in the docetaxel followed by castration group. As in other studies, the bax-to-bcl-2 ratio decreased following cas-

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KEY POINTS

- The established therapeutic limitation of ADT coupled with the biologic heterogeneity of prostate cancer with the presence of androgen-sensitive and androgen-insensitive clones provide the rationale for a preemptive multitargeted strategy with the addition of chemotherapy to ADT.
- Before docetaxel, trials investigating the addition of different chemotherapy regimens to ADT in mHSPC did not show significant benefits.
- The proven efficacy of docetaxel in the castration-resistant setting provided rationale to investigate this drug earlier in the course of the disease.
- Results of E3805 (CHAARTED trial), a phase III clinical trial conducted in patients with mHSPC comparing ADT alone to ADT plus docetaxel chemotherapy, demonstrated a significant 13.6-month improvement in median overall survival for the chemo-hormonal approach. Importantly, in patients with high-volume disease, there is a 17-month survival improvement for ADT plus docetaxel. In patients with low-volume disease, longer follow-up is needed to assess effect.
- Six cycles of docetaxel in addition to ADT is an appropriate therapeutic approach for men with newly diagnosed mHSPC initiating ADT, particularly those with high volume disease, and who are otherwise medically candidates for docetaxel therapy.
- Emerging data suggest that sequential use of current AR targeted agents in metastatic castration resistant prostate cancer (mCRPC) is not associated with optimal efficacy. The latter coupled with disease related impact on performance status and medical condition provides the rational for integrating docetaxel chemotherapy earlier in the treatment course of patients with mCRPC.

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tration. However, the bax-to-bcl-2 ratio remained increased following docetaxel, indicating increased apoptosis.[17]

Numerous AR-independent intracellular oncogenic pathways including MAPK, RB1, and PI3K/AKT/mTOR are dysregulated through a variety of mechanisms in advanced prostate cancer. Downstream effects of genetic alterations in these pathways promote survival, proliferation, cell-cycle progression, and conversely regulate AR signaling through feedback mechanisms.[18-23] Chemotherapy may attack cells with AR-independent signaling pathways driving mechanisms of castration resistance. Considering the biologic observations and the experience in prostate cancer and other cancers, it is logical to hypothesize that earlier use of effective systemic therapies could result in a more significant impact in hormone-sensitive disease.

CLINICAL TRIALS OF CHEMOTHERAPY IN MHSPC

The initial trials investigating the combination of chemotherapy with ADT in mHSPC did not show overall survival advantage. Since the 1970s, more than 10 randomized studies were conducted investigating different chemotherapy drugs in combination with ADT. Regimens included a variety of cytotoxic drugs such as cyclophosphamide, estramustine, doxorubicin, fluorouracil, mitomycin, and vinblastine, but failed to demonstrate a significant survival benefit when combined with ADT in metastatic prostate cancer[24-33] (Table 1). However, there were some hints with regard to potential benefits of chemotherapy in specific subgroups of patients. Murphy et al conducted a randomized trial comparing diethylstilbestrol (DES) or orchiectomy, DES plus cyclophosph-

TABLE 1. Early Clinical Trials of Androgen Deprivation Therapy with or without Chemotherapy in Hormone-Naive Metastatic Prostate Cancer

First Author and Accrual	No. of Patients	Treatment Arms	Median PFS (Months)	Median OS (Months)
Murphy[24], 1976–1980	246	A: DES/orch	Not reported	23 mo in all arms
		B: DES + CTX		
		C: CTX + estramustine		
Murphy[25], 1980–1983	319	A: DES/orch	15 mo in all arms	33 mo in all arms
		B: CTX + 5FU + DES		
		C: Estramustine		
Osborne[26], 1982–1986	143	A: DES/orch	A: 15	A: 25.6
		B: DES/orch + CTX + Dox	B: 18	B: 22.0
			(p = 0.8)	(p = 0.55)
Pummer[27], 1988–1991	145	A: Flut/orch	A: 12	A: 18
		B: Flut/orch + epirubicin	B: 22	B: 30
			(p = <0.02)	(p = 0.12)
Janknegt[28], 1989–1990	419	A: Orchiectomy	A: 17	A: 24
		B: Orch + estramustine	B: 24	B: 27
			(p = 0.3)	(NS)
Boel[29], 1988–1991	148	A: Orchiectomy	A: 29	A: 31
		B: Orch + mitomycin C	B: 26	B: 31
			(p = 0.64)	(NS)
De Reijke[30], 1990–1995	189	A: Orchiectomy	A: 12	A: 26
		B: Orch + mitomycin C	B: 12	B: 22
			(p = 0.67)	(p = 0.04)
Kuriyama[31], 1990–1992	136	A: DES or orchiectomy	A: 30	A: 67
		B: DES or orch + UFT	B: 72	B: >96
			(p = .06)	(p = 0.13)
Noguchi[32], 1995–1998	51	A: LHRH + FLT	A: 14.6	A: 30
		B: LHRH + estramustine	B: 25.4	B: 30
			(p = 0.03)	(NS)
Millikan[33], 1996–2003	286	A: LHRH or orch	A: 24	A: 64
		B: LHRH/orch + ketoc + dox + vinb + estramustine (KAVE regimen)	B: 35	B: 72
			(p = 0.39)	(p = 0.41)

Abbreviations: orch, bilateral orchiectomy; DES, diethylstilbestrol; dox, doxorubicin; NS, not significant; LHRH, super agonist of luteinizing hormone-releasing hormone; CTX, cyclophosphamide; FU, fluorouracil; UFT, uracil plus tegafur (an oral fluoropyrimidine); FLT, flutamide; ketoc, ketoconazole; vinb, vinblastine.
Adapted from Millikan et al.[33]

amide, or estramustine plus cyclophosphamide in patients with newly diagnosed metastatic prostate cancer. There was no overall survival difference between the three groups (92, 91, and 94 weeks, respectively); however, subgroup analysis within groups having pain versus those not having pain showed a survival benefit for the cyclophosphamide and estramustine arm in patients presenting with pain at study entry.[24] Osborne et al compared endocrine therapy alone (DES or orchiectomy) to a chemo-endocrine approach (DES plus cyclophosphamide/doxorubicin hydrochloride) in a randomized trial lead by SWOG.[26] Although there was a higher response rate in the chemo-endocrine group (63%) compared with endocrine alone (48%), this effect did not translate to a significant difference in overall survival. Epirubicin has also been studied in this setting. A prospective randomized trial conducted by Pummer et al investigated the addition of weekly epirubicin to androgen blockade (orchiectomy and flutamide) for 18 weeks.[27] At a median follow-up of 81 months, the chemo-hormonal arm showed a significant benefit in progression-free survival (PFS;18 months) compared with the hormonal arm (12 months, p < 0.02). However, there were no OS differences between the groups. In patients with more than five sites of bone metastasis, PFS was 9 and 14 months (p = 0.005) and OS, 17 and 27 months (p = 0.06), respectively. Estramustine has also been tested in addition to hormone therapy in patients with newly diagnosed metastatic prostate cancer without evidence of survival advantage. In subgroup analysis, estramustine prolonged time to progression when added to orchiectomy in patients with bone metastasis.[28]

More recently, Millikan et al conducted a phase III clinical trial investigating the addition of ketoconazole, doxorubicin, vinblastine, and estramustine (KAVE regimen) to androgen ablation therapy.[33] The primary endpoint of time to castrate-resistant progression was 24 months for the androgen ablation arm, and 35 months for the chemo-hormone therapy (p = 0.39). Median overall survival was not different between the groups (5.4 and 6.1 years, respectively). Similar to other trials, time to progression was significantly delayed in the high-volume group but not in those with less advanced disease. In patients with high-volume disease (three or more bone lesions or visceral involvement) the median time to progression was 11.2 months in the control group and 20.5 months in the KAVE arm (p = 0.08). Nearly all patients (in either arm) did receive cytotoxic therapy for castrate-resistant disease, usually including a taxane.[33]

Most of these trials had substantial limitations in design, sample size, and most importantly, used chemotherapy drugs without significant clinical activity in advanced prostate cancer. Specifically, none of the trials included cytotoxic chemotherapy that prolonged survival in the castration-resistant setting.

DOCETAXEL: FIRST AGENT TO IMPROVE SURVIVAL IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Docetaxel, a taxane chemotherapeutic drug, induces polymerization of microtubules and phosphorylation of the bcl-2

protein.[34] Docetaxel was approved in castration-resistant prostate cancer after two randomized landmark studies, TAX 327 and SWOG-9916, independently demonstrated improvements in overall survival in men with mCRPC.[5,6] Docetaxel triumphed over the longstanding paradigm that prostate cancer cells were resistant to cytotoxic agents. The TAX 327 study reported an improved overall survival of the group treated with docetaxel every 3 weeks (18.9 months) compared to the group treated with mitoxantrone (16.5 months). The hazard ratio for death of docetaxel compared with mitoxantrone was 0.83 (95% CI, 0.70 to 0.99; p = 0.04). Quality of life was also significantly improved in the group treated with docetaxel.[5] Petrylak et al reported a similar improvement in survival for docetaxel plus estramustine in comparison with mitoxantrone plus prednisone in the SWOG-9916 study.[6] The median overall survival was 17.5 months in those treated with docetaxel-based therapy versus 15.6 months in patients in the mitoxantrone group (p < 0.001). Docetaxel became the standard of care for men with CRPC in 2004.

The role of chemotherapy in prostate cancer management was further supported by the approval of a third chemotherapy agent, cabazitaxel, which is also an inhibitor of microtubule depolymerization based on improving survival in a phase III trial in patients with CRPC previously treated with docetaxel as compared to mitoxantrone (15.1 vs. 12.7 months; 95% CI, 0.61 to 0.84).[7] The risk of death was significantly lower in those patients treated with cabazitaxel versus patients treated with mitoxantrone (HR 0.70; p < 0.0001). Cabazitaxel received U.S. Food and Drug Administration (FDA)-approval in 2010 for men with CRPC that had progressed on docetaxel.

RANDOMIZED CLINICAL TRIALS OF EARLY DOCETAXEL PLUS ADT

The use of docetaxel in the mHSPC setting was driven by its established activity in two phase III randomized clinical trials demonstrating a survival advantage as compared with an active control of mitoxantrone. The underlying premise is that an agent with clinical benefit in mCRPC might prolong the lives of men with mHSPC if used before the disease becomes resistant to ADT and to attack the de novo androgen resistant/independent clones much earlier. There are also emerging data that docetaxel may act as a hormonal agent, interfering with androgen receptor (AR) nuclear translocation on microtubules.[35]

Two phase III clinical trials were designed to evaluate the role of docetaxel in mHSPC (Table 2). GETUG-AFU 15 was a randomized, open-label, phase III trial that enrolled 385 patients with newly diagnosed mHSPC.[36] In this study, patients were randomly assigned to receive ADT alone (orchiectomy or LHRH agonists) or in combination with docetaxel (75 mg/m² on day 1 of a 3-week cycle; nine planned cycles). The median number of docetaxel cycles was eight. With median follow-up of 50 months, there was a trend in favor of do-

TABLE 2. Randomized Clinical Trials of ADT with or without Docetaxel in Hormone-Naive Metastatic Prostate Cancer

Trial, Accrual Period	No. of Patients	Median Follow-up (Months)	Treatment Arms	Median PFS (Months)	Median OS (Months)
GETUG-AFU 15[36], 2004–2008	385	82.9	A: ADT	A: 12.9	A: 46.5
			B: ADT+ docetaxel for 6 cycles	B: 22.9	B: 60.9
				(HR = 0.72, p = 0.0021)	(HR = 0.9, p = 0.44)
E3805: CHAARTED[38], 2006–2012	790	29	A: ADT	A: 19.8	A: 44
			B: ADT + docetaxel for 6 cycles	B: 32.7	B: 57.6
				(HR = 0.49; p = <0.0001)	(HR = 0.61; p = 0.0003)

Abbreviations: PFS, progression-free survival; OS, overall survival; ADT, androgen-deprivation therapy; HR, hazard ratio.

cetaxel; however, the primary endpoint of overall survival was not significantly different between the groups at 58.9 months for patients that received docetaxel plus ADT versus 54.2 months for those who were treated with ADT alone (HR 1.01; 95% CI, 0.75 to 1.36; p = 0.955). On the contrary, the addition of docetaxel to ADT did significantly improve the biochemical PFS (secondary endpoint), which was 22.9 months for the combined treatment group and 12.9 months for those treated with ADT alone (HR 0.72; 95% CI, 0.57 to 0.91; p = 0.005). Seventy-two serious adverse events were reported in the group given ADT plus docetaxel: more frequently neutropenia (21%), febrile neutropenia (3%), abnormal liver function tests (2%), and neutropenia with infection (1%). Four treatment-related deaths occurred in the ADT plus docetaxel group. An updated report with longer follow-up of the GETUG-AFU 15 trial was presented at the 2015 Genitourinary Cancers Symposium.[36] With a median follow-up of 82.9 months, the median OS was 60.9 months and 46.5 months in the ADT plus docetaxel and ADT alone arms, respectively (HR 0.9; 95% CI, 0.7 to 1.2; p = 0.44). In patients with high-volume disease, median OS rates were 39 months in ADT plus docetaxel arm and 35.1 months in the ADT alone arm (HR 0.8; 95% CI, 0.6 to 1.2; p = 0.35).[36]

The GETUG-AFU 15 trial did not show statistically significant survival benefit to adding docetaxel to ADT for mHSPC. However, the overall survival trend and the HR in the high-volume patients favors the docetaxel arm. The trial had a relatively small sample size,[1] included a substantial percentage of patients with good prognostic factors at baseline: 49% of the patients in the ADT plus docetaxel group and 50% of the patients treated with ADT alone. Another concern about this trial is the unusually high toxicity reported, with more than 10% incidence of grade 3 neutropenia and four deaths in the group given ADT plus docetaxel; 21% of men who received docetaxel plus ADT discontinued treatment because of toxicity. Results may have also been affected by cross-over treatments since 62% of patients given ADT alone received docetaxel at progression, compared with 28% of patients given ADT plus docetaxel who were re-treated with docetaxel. Interestingly, the Kaplan-Meier curves for overall survival seem to separate after 36 months of follow-up. How-

ever, only 199 patients are at risk at 36 months, and 124 at 48 months.

Data Presented at the 2014 ASCO Annual Meeting Plenary Session

The results of the E3805 (Chemo-Hormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer [CHAARTED]) trial recently reported by Sweeney et al[37] provide practice-changing evidence. CHAARTED is a U.S. intergroup phase III trial in which 790 men with hormone-naive mHSPC received either ADT alone or ADT with 75 mg/m^2 of docetaxel every 3 weeks for a maximum of six cycles. At enrollment, patients were stratified by extent of metastatic disease as high-volume or low-volume; high volume was defined as visceral metastasis and/or four or more bone metastases with at least one beyond axial skeleton (pelvis and vertebral column). The primary endpoint was OS, and secondary endpoints included time to biochemical, radiographic, or symptomatic progressive disease (PD) and time to radiographic or symptomatic PD. The trial was first designed to include high-volume patients as they have poor prognosis. Eligibility was subsequently expanded to allow all patients with mHSPC.

The addition of docetaxel to ADT significantly improved overall survival; a median of 57.6 months in the ADT plus docetaxel arm and 44.0 months in the ADT arm (HR 0.61; 95% CI, 0.47 to 0.80; p = 0.0003). The survival improvement was seen specifically in men with high-volume disease; median OS was 49.2 months with docetaxel plus ADT compared with 32.2 months with ADT, a difference of 17 months (HR 0.60; 95% CI, 0.45 to 0.81; p = 0.0006). In men with low-volume disease, median OS had not been reached at the time of the presentation. The secondary endpoints demonstrated higher PSA responses (< 0.2 ng/mL) at 6 and 12 months in the docetaxel plus ADT group (27.5% and 22.7%, respectively) compared to the ADT alone group (14% and 11.7%, respectively), longer median time to castration resistance (20.7 months vs. 14.7 months) and longer median time to clinical progression in favor or the combination arm; 32.7 months, compared to 19.8 months (p < 0.0001).

With regard to toxicity, 6% of men receiving docetaxel plus ADT experienced febrile neutropenia, 1% experienced sig-

nificant effects on sensory nerves, and 1% on motor nerves, and 1 of the 397 patients who received early docetaxel died as a result of treatment. The cause of death was prostate cancer in 84 patients in the ADT plus docetaxel arm (83.2%) and 112 patients in the ADT-alone arm (83.6%).[37]

In summary, this study shows that starting docetaxel along with hormone therapy in men with newly diagnosed hormone-sensitive prostate cancer improved OS by more than 13.6 months in comparison with standard hormone therapy alone. The bulk of the benefit appears to be in patients with high-volume disease. This striking survival benefit supports the use of upfront docetaxel in hormone-sensitive prostate cancer, especially in patients with high-volume disease.

Before CHAARTED, docetaxel was reserved for patients relapsing after initial ADT. In that setting, docetaxel produced only 2 to 3 months prolongation of survival. More recently, abiraterone, enzalutamide, and radium-223 also produce 3- to 5-month prolongations of median survival when they are given as successive single agents. The magnitude of survival improvement with docetaxel plus ADT upfront is unprecedented. The most likely explanation is biologic; therapy works best when it is multitargeted, administered in a lesser disease volume as a preemptive strike before adaptive resistance. Other potential factors include better drug tolerance and less toxicity in less sick patients.

CONCLUSION

The heterogeneity of prostate cancer and the diverse mechanisms of resistance support a multitargeted approach to maximize the antitumor impact. The totality of the current data would favor not delaying the use of docetaxel chemotherapy; pending the final peer-review publication of the CHAARTED trial, results strongly suggest that survival benefits of docetaxel are significantly higher when given in combination with ADT early in the course of mHSPC and that the combination has a more profound return on investment as compared with sequential therapy. The unprecedented survival benefits of this chemo-hormonal approach appear to be related to the better antitumor effect as reflected by higher rates of undetectable PSA levels and longer median time to castration resistance and clinical progression. Overall, patients tolerated therapy very well. Therefore, patients with newly diagnosed mHSPC who are deemed chemotherapy eligible, especially those with high-volume disease, should be counseled regarding this data and offered combination therapy.

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Radium 223: How Can We Optimize This New Tool for Metastatic Castration-Resistant Prostate Cancer?

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OVERVIEW

Radium 223 is an alpha-emitting intravenous radiotherapy approved for the treatment of men with metastatic castration-resistant prostate cancer (mCRPC). The approved indication covers men with pain from bony metastatic disease and no visceral involvement; however, questions remain as to optimal patient selection and timing of this treatment relative to other life-extending therapies for mCRPC. Limited data exist to guide clinicians on how to position radium 223 in the therapeutic sequence, however, some theoretical considerations and data derived from the ALSYMPCA trial populations pre- and postdocetaxel will be outlined. Subgroup analyses may provide some insight into patient selection.

Radium 223 is a calcium-mimetic alpha-emitting radio-pharmaceutical that was approved by the U.S. Food and Drug Administration for the management of mCRPC in 2013. Unlike previous radiopharmaceuticals, such as samarium-153-lexidronam and strontium chloride Sr 89 that provide pain palliation without having a known effect on survival,[1,2] radium 223 has been found to prolong survival in patients with mCRPC.[3] The approved dosing of radium 223 is 50 kBq/kg given intravenously over 1 minute every 28 days for 6 doses. Questions remain as to its optimal application, particularly in terms of patient selection and sequencing of this therapy relative to other approved life-extending therapies for mCRPC. There are a paucity of real-world data, and key limitations for the use of radiopharmaceuticals include special licensing requirements to administer therapy and lack of comparative data. Ongoing studies aim to address questions of sequence and combination, but we will discuss patient selection and timing for radium 223 therapy in the context of the limited available data.

WHICH PATIENTS?

The ALSYMPCA trial randomly assigned 928 men with pain of any intensity related to bone metastases from mCRPC and whose disease had either progressed on docetaxel or who were not docetaxel candidates, to receive 50 kBq/kg of radium 223 intravenously over 1 minute each month for 6 doses or placebo IV each month for 6 doses in conjunction with standard care (Table 1).[3] Men with known visceral metastases were excluded, but malignant lymphadenopathy smaller than 3 cm in short axis diameter was allowed. Adequate hematologic function is required. Before the first administration of radium 223, the abso-

lute neutrophil count was 1.5×10^9/L or higher, the platelet count was 100×10^9/L or higher, and hemoglobin was 10 g/dL or higher. Before subsequent administrations of radium 223, the absolute neutrophil count was 1×10^9/L or higher and the platelet count was 50×10^9/L or higher. The primary endpoint was overall survival and the main secondary endpoint was time to symptomatic skeletal-related event (sSRE). Most patients (58%) had received docetaxel, and 41% had received bisphosphonate therapy.

A significant increase in overall survival was observed across all patients treated with radium 223 (hazard ratio [HR] 0.7; 95% CI, 0.58 to 0.83; p < 0.001), however, analysis of subsets may help clarify the characteristics of optimal candidates for this treatment based on blood or imaging biomarkers. Serum alkaline phosphatase, one marker of overall osteoblastic activity, did seem to define patients who benefited the most from radium 223 treatment. Specifically, no increase in overall survival was seen in the subgroup treated with less than 220 U/L of serum alkaline phosphatase. In contrast, there was no clear separation of radium 223 benefit according to the extent of disease as defined by the number of lesions on the bone scintigraphy. Although subgroup analysis revealed a statistically significant (HR 0.95; 95% CI, 0.46 to 1.95 for < 6 bone metastases; no p value given) survival benefit with radium 223 for men with more than six bone metastases, the subgroups of men with two to six metastases or superscan had confidence intervals crossing 1, calling into question the benefit of therapy for these subgroups. Although small group sizes may limit the strength of these subset analyses, the results do validate continuing efforts to better define patient groups who are most likely to benefit from this treatment.

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Disclosures of potential conflicts of interest are found at the end of this article.

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Table 1. Clinical Characteristics of Patients Eligible versus Optimal for Radium 223

Eligible Patients	Optimal Patients
Two or more bone metastases	More than 6 bone metastases
Pain from bone metastases	Serum alkaline phosphatase greater than or equal to 220 U/L
Adequate marrow reserve	Concurrent bisphosphonate use
No visceral metastases	Question not in the setting of "superscan"
Prior docetaxel (or ineligible/ declined docetaxel)	

TIMING OF RADIUM 223 VERSUS CHEMOTHERAPY OR OTHER TREATMENT OPTIONS

The treatment landscape for patients with symptomatic CRPC is complex and manifested by the availability of a wide array of therapeutic modalities ranging from oral androgen inhibitors, cytotoxic chemotherapy, and external beam radiotherapy as well as radium 223. Although radium 223 may have a place in treatment for many patients with symptomatic CRPC, timing its use in a treatment sequence for any specific patient presents a challenging decision for a treating physician. Given the potential for additive and long-term myelosuppression associated with bone-target radiopharmaceuticals and cytotoxic chemotherapy, most of the available analyses focus on the timing of radium 223 before or after docetaxel-based chemotherapy.

Tolerability of radium 223 was similar in men who had received chemotherapy first and in those who declined or were not felt to be eligible for chemotherapy. A retrospective analysis from ALSYMPCA identified modestly higher rates of hematologic toxicity in docetaxel-pretreated patients receiving radium 223 compared with those not previously treated with docetaxel (Table 2). There was also a higher rate of packed red blood cell transfusion, which persisted during the 13-week time period after completion of the sixth cycle of radium 223 therapy.[4] Nonhematologic toxicities were similar in the two groups, although there was more nausea (40% vs.

KEY POINTS

- Radium 223 delays time to symptomatic skeletal-related events and prolongs overall survival for men with mCRPC and more than two bone metastases with pain attributed to bone metastases.
- Greater benefit may occur in subgroups of men with more than six bone metastases and elevated serum alkaline phosphatase over 220 U/L.
- There is a modestly higher rate of hematologic toxicity in men receiving radium 223 after previous docetaxel therapy, but no data exist regarding the effect of radium 223 on bone marrow reserve for subsequent chemotherapy.
- Follow-up data are limited regarding the possibility of long-term myelosuppression and secondary myelodysplasia or leukemia.
- Prostate-specific antigen changes should not be used to determine response to treatment or duration of treatment.

Table 2. Rates and Grades of Hematologic Toxicity in Patients Receiving Radium 223 by Prior Docetaxel Therapy Status

	Prior Docetaxel (347 Patients)	No Prior Docetaxel (253 Patients)
Anemia		
All grades	120 (35%)	67 (27%)
Grade 3	42 (12%)	24 (10%)
Grade 4	8 (2%)	3 (1%)
Grade 5	0	0
Neutropenia		
All grades	24 (7%)	6 (2%)
Grade 3	8 (2%)	1 (<1%)
Grade 4	3 (1%)	1 (<1%)
Grade 5	0	0
Thrombocytopenia		
All grades	53 (15%)	16 (6%)
Grade 3	15 (4%)	5 (2%)
Grade 4	16 (5%)	2 (1%)
Grade 5	0	1 (<1%)

30%) and vomiting (24% vs. 11%) for docetaxel-pretreated compared with nonpretreated patients.

Efficacy of radium 223 was seen in both docetaxel-pretreated and docetaxel-naive patients in ALSYMPCA. However, subgroup analysis did identify that symptomatic skeletal events were not substantially delayed in the docetaxel-naive group.[5] Specifically, the median time to sSRE was 17 months for patients treated with radium 223 and 19.5 months for placebo in docetaxel-naive patients (p = 0.12), whereas the median time to sSRE was 13.5 months in the radium 223 group compared with 7.8 months for placebo in docetaxel-pretreated patients (p = 0.00087). Although this is a subgroup analysis, and this finding warrants caution in interpretation, it may be that patients pretreated with docetaxel with bone pain represent an enriched, more aggressive subgroup in which bone targeting therapy may yield a greater effect.

In terms of the tolerability of chemotherapy after radium 223, no published data exist regarding how many men treated with radium 223 went on to receive docetaxel (or other chemotherapy) and how they tolerated therapy in terms of myelosuppression. This may be because of the fact that enrollment in ALSYMPCA was restricted to men who had either received docetaxel or were not eligible for *or* declined docetaxel therapy such that there may be limited numbers of patients from this trial who subsequently received docetaxel. As noted above, the increased need for blood transfusions persisted in the 13 weeks following completion of radium 223 therapy, which suggests that tolerance of chemotherapy may be affected, at least in the short term. Thus the potential for higher rate of hematologic toxicity during radium 223 treatment when docetaxel has been administered first must be considered against the possibility that radium

223 may confer fewer benefits when administered first, before docetaxel as well as against the theoretical concern for compromised marrow reserve affecting future docetaxel therapy. Data are still awaited to answer these questions with greater certainty. However, given the relatively mild myelosuppression and previous experience with samarium in combination with docetaxel, combination therapy is undergoing study (NCT01106352). In the phase I experience of radium 223 and docetaxel, substantial hematologic toxicity limited administration of full doses and thus further combination studies will utilize a reduced dose of docetaxel 60 mg/m^2.[6]

Another significant concern when the potential for earlier administration is considered is the risk of secondary myelodysplasia. Very limited long-term data are currently available. The long-term report presented at 2014 American Society of Clinical Oncology Genitourinary Cancers Symposium consisted of median follow-up of 10.4 months.[7] At that time point, no myelodysplastic syndrome or acute myeloid leukemia had been reported, and secondary solid tumors were similar in the radium 223 and placebo arms. However, longer follow-up will be critical to address this concern.

Much less is known about the timing and interaction between radium 223 and the newer antiandrogen agents (abiraterone or enzalutamide). Both agents have demonstrated noteworthy clinical activity defined by increases in overall survival in patient subsets defined by the presence of cancer-related bone pain. Further, both agents have shown important benefits in quality-of-life measures including palliation in bone pain or delay to skeletal-related events in certain patient subpopulations.[8,9] ALSYMPCA allowed standard care, including ketoconazole and older androgen receptor antagonists, but this cannot be extrapolated to assume that newer agents such as abiraterone and enzalutamide can be safely combined with radium 223. No data exist to suggest that combination use is superior to single sequential therapy. The open-access protocol did allow abiraterone, and the safety and efficacy of these combinations will be formally evaluated in an ongoing clinical trial (NCT02034552).

DURATION

Just as questions emerge as to the optimal timing for initiation of radium 223 dichloride, many questions also arise as to when it should be discontinued. The approved treatment course is 6 monthly doses, although the relative efficacy and tolerability of fewer or more doses is not well established. At the time of the *New England Journal of Medicine* publication from the ALSYMPCA trial,[3] 42% of patients on the radium 223 arm had not received all 6 doses although the median number of doses was 6; updated data regarding clinical factors associated with completion of the treatment course may be helpful. The phase I study evaluated a single dose in patients with breast and prostate cancer with bone metastases and the phase II study in prostate cancer gave 4 doses at monthly intervals,[10,11] but there is no way to evaluate what number of doses is optimal from the available data. Given that no cumulative toxicities were seen with 6 monthly doses, and the rate of hematologic toxicities was tolerable, it is reasonable to explore the effect of additional dosing on disease control and the duration of pain palliation. The effect of extended therapy with up to 6 additional doses, or a total of 12 doses of radium 223, is being evaluated in a clinical trial (NCT01934790). Additionally, we do not have data about retreatment of patients who were previously treated. Thus at this time no conclusions can be made as to the efficacy nor safety of more than 6 monthly doses of radium 223.

Effectiveness may be difficult to gauge during the nominal 6-month treatment period. Prostate-specific antigen (PSA) is an unreliable marker of response to radium 223 as it often continues to increase (unabated) during the treatment independent to the effect on overall survival. In the ALSYMPCA trial the median time to PSA progression was 3.6 months for men in the radium 223 arm compared with 3.4 months in the control arm (HR 0.64; 95% CI, 0.54 to 0.77) and 16% achieved a PSA decline at 12 weeks compared with 6% of control patients. These PSA changes must be viewed in the context that the patients could receive additional standard therapy (in ALSYMPCA, standard care could include antiandrogens, ketoconazole, estrogens, and external beam radiotherapy). Nevertheless, discontinuation of radium 223 in patients with rising PSA but no clinical disease progression is not indicated, and rather application of additional standard therapy may be considered. Thus, even in patients without early pain relief from radium 223 or with rising PSA, it may be preferable to add external beam radiotherapy or additional systemic therapy, and proceed through the course of 6 doses rather than stopping therapy early.

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GENITOURINARY CANCER

Immunotherapy for Genitourinary Tumors: Are We Ready for Prime Time?

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Immunotherapeutic Approaches in Prostate Cancer: Combinations and Clinical Integration

Susan F. Slovin, MD, PhD

OVERVIEW

Despite multiple immunologic approaches with peptide, protein, and DNA vaccines, no single therapy has induced complete remission or maintained durability of response in patients with castration-resistant prostate cancer (CRPC). Historically, immunotherapy has had limited effect on solid tumors with the exception of melanoma and renal cell carcinomas, which have been deemed as immunologic cancers given their potential for remissions either spontaneously or after removal of the primary lesion. There is considerable excitement about using an immunotherapy in combination with biologic agents such as checkpoint inhibitors, cytokines, other vaccines, or chemotherapy. Sipuleucel-T represents one of several novel immunologic therapeutic approaches to treat prostate cancer in addition to other solid tumors. It is the first in its class of autologous cellular therapies to demonstrate safety and an overall survival benefit in patients with asymptomatic or minimally symptomatic CRPC and represents a unique treatment method that may be further enhanced with other agents. Although sipuleucel-T can be used as a foundation on which to build and enhance future immunologic clinical trials, other exciting strategies are in development that may be easily integrated into the algorithm of current care.

The introduction of immunotherapy for the treatment of CRPC has been transformative in that it has revitalized an area of research that had waned for many years. Although there are five new therapies that have changed the standard treatment algorithms used for treating CRPC, a personalized medicine approach is now being embraced as a means of developing and directing therapies based on unique patient molecular profiling and the ability to target actionable mutations with specific drugs. Despite the enthusiasm held for immunotherapy, there are still concerns about how to best integrate a specific type of immunotherapy into the current treatment algorithm and whether combinatorial approaches will improve antitumor responses. Jerome Groopman, MD,[1] a well-known physician who on occasion presents his views on controversial medical issues in *The New Yorker* magazine, has noted that there are many new oncology drugs now available to patients with different cancers, but the question remains whether it is possible to "control cancer without killing it." Immunotherapy may in fact provide sufficient control in prostate cancer that may minimize the need for immediate cytotoxic agents.

Immunotherapy for solid tumors is not new; preclinical studies have suggested that animals can be cured with a wide variety of approaches from conjugate and DNA vaccines, to combinatorial schemes with chemotherapy or biologic modifiers. However, stunningly successful preclinical vaccine strategies have not successfully translated into similar results in humans. Each of the five new drugs approved for prostate cancer—sipuleucel-T,[2] enzalutamide,[3,4] abiraterone,[5] cabazitaxel,[6] and radium 223 dichloride[7]—has shown a survival benefit, benefits in pain control, and quality of life, but sipuleucel-T has revitalized the role of immunotherapy in treating a solid tumor. Sipuleucel-T stands out as the first immunotherapy approved by the U.S. Food and Drug Administration (FDA) for prostate cancer with the added benefit of improvement in overall survival (OS).[2] Its approval was determined by the results of a placebo-controlled, randomized trial (the IMPACT trial),[2] conducted in 512 asymptomatic or minimally symptomatic men with metastatic CRPC. Although no difference in time to progression or prostate-specific antigen (PSA) response rate was reported, a significant 4.1-month improvement in median survival was achieved in the active arm compared with the placebo arm (25.8 vs. 21.7 months; p = 0.03). The survival benefit was comparable to that seen with other standard agents.[3-7] In fact, given how many of the androgen receptor (AR)-directed therapies have been introduced earlier in the treatment paradigm, the same may prove beneficial with immune-based therapies. Although sipuleucel-T's indication is for patients with asymptomatic or minimally symptomatic CRPC, it has broad applicability to all clinical states of the disease, that is, from neoadjuvant, to biochemical relapse post-primary therapy, to castrate nonmetastatic disease, and castrate metastatic disease.[7]

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Disclosures of potential conflicts of interest are found at the end of this article.

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CHANGING THE TREATMENT PARADIGM

Sipuleucel-T is an autologous cellular product vaccine that mandates that patients undergo leukapheresis to obtain peripheral blood mononuclear cells that are processed, expanded, and incubated with a prostatic acid phosphatase (PAP)/granulocyte macrophage-colony stimulating factor (GM-CSF) fusion protein within a 48-hour window. The cells are divided into three reinfusions, one given every 2 weeks. In clinical trials, patients were then monitored per clinical practice with imaging and PSAs. Overall, the treatment was well tolerated with expected transfusion-associated side effects such as fever and chills. Since the FDA approval of sipuleucel-T, additional studies have sought to expand its use and to identify in which patients the greatest clinical benefits may be derived. A retrospective analysis of the IMPACT trial found that patients in the lowest quartile of PSA values derived a greater benefit from sipuleucel-T with a 13-month improvement in OS (41.3 months with sipuleucel-T compared with 28.3 months with placebo; [HR 0.51; 95% CI, 0.35 to 0.85]). However, for those patients in the highest baseline PSA quartile, the median OS was 18.4 months compared with 15.6 months for placebo (HR 0.84; 95% CI, 0.55 to 1.29), with an improvement of only 2.8 months.[8] Most of the studies of sipuleucel-T have been retrospective and its mechanism of action is still controversial. A report by Drake et al[9] postulated that antigen cascade (Fig. 1) may be responsible for its mechanism of action. This also is thought to be a key factor for ProstVAC.[10] Though antibodies to PAP were generated, and a robust ki57 proliferative response was induced, this may be suggestive of an adaptive immune response. Additional evaluation of retrospective studies by Drake et al[9] suggested that OS was improved in patients who received sipuleucel-T and had immunoglobin G antibody responses to greater than two secondary antigens compared with those patients who did generate antibodies. It should be noted that

the term response should be used within the context of an association of antibody induction with a change in biology of the cancer, that is, clinical outcome, and not the generation of the antibody in response to an immunogen per se. Similarly, a caveat in determining whether there is an effect of the immune therapy on either the humoral or cellular compartments is that any induction of a component of either compartment, that is, antibody or T cell population, should correlate with a biologic change in the cancer.

Sipuleucel-T has been met with enthusiasm as the first immunotherapy approved for a solid tumor malignancy; the observation that OS was improved in the absence of significant clinical benefit has encouraged further evaluation of the mechanism for survival benefit and whether, over time, a significant antitumor response could be induced. Many physicians in the field felt that knowing the mechanism of action was important for future clinical trial development; whereas, others felt that knowing the mechanism of action made little difference in their use of the drug as long as the drug provided some clinical benefit. As such, investigators have sought to identify a biomarker that may indicate that a target has been hit or that the immune system has been stimulated. Because of mixed cellular nature of the autologous mononuclear cell product, it was unclear as to the nature of the effector population that may have been relevant in inducing a potential antitumor effect, and ultimately survival. Other than T-cell–proliferation assays, no other cellular marker was indicative of this product inducing immunogenicity. The working premise has always been that the cellular product was enriched with antigen presenting cells (APC). This was confirmed by the observation by flow cytometry that CD54+ cells were responsible for antigen uptake and that CD54+ cells harbored the PAP-specific antigen presentation activity as assayed using a PAP-specific HLA-DRβ1–restricted T cell hydridoma.[11,12] The marker CD54 or intracellular adhesion molecule-1 (ICAM-1) serves as a ligand for the CD11a/CD18 (LFA-1) leukocyte integrin complex, and its interaction with other cells types is thought to be relevant in its role as a potential costimulatory receptor.[11,13,14] In the setting of sipuleucel-T, the fusion protein, PA2024, comprised of PAP fused to GM-CSF was used as the immunogen, with the PAP portion of the molecule providing the necessary immunogenicity and the GM-CSF serving to activate the APC. Studies confirmed that the isolated CD54+ cells took up the antigen as well as presented and processed the antigen in an MHC-restricted manner.[11] Similar results were obtained with an HLA-DRβ1 restricted T cell hybridoma specific for a different PAP-derived peptide. These findings provided some insight to how the product might work in vivo but still required validation. This was later confirmed. The opportunity to further validate the earlier role of CD54+ cells was provided by the availability of cellular products from three phase III double-blind, placebo-controlled trials in patients with metastatic CRPC including the IMPACT trial, which led to the product's FDA approval. Patients were randomly selected 2:1 in favor of sipuleucel-T or to control. This included a minimum of at least one treatment with the cellular product as

KEY POINTS

- Sipuleucel-T remains a standard for patients with asymptomatic or minimally symptomatic castration-resistant prostate cancer.
- The checkpoint inhibitor ipilimumab has shown activity in phase I, II, and III trials in patients with prostate cancer with durable responses; however, the phase III trial did not show a survival benefit.
- A subset analysis of patients with castration-resistant prostate cancer who had visceral metastases did not show a survival benefit with ipilimumab and radiation, suggesting that there may be some advantage to patients without visceral metastases.
- Future work with combination approaches with immunotherapy, including chimeric antigen receptor-directed T lymphocytes, represents novel approaches.
- Establishment of appropriate immunologic biomarkers that are associated with disease response/outcome is needed.

FIGURE 1. Graphic Describing Antigen Spreading by Banderlugt and Miller[67]
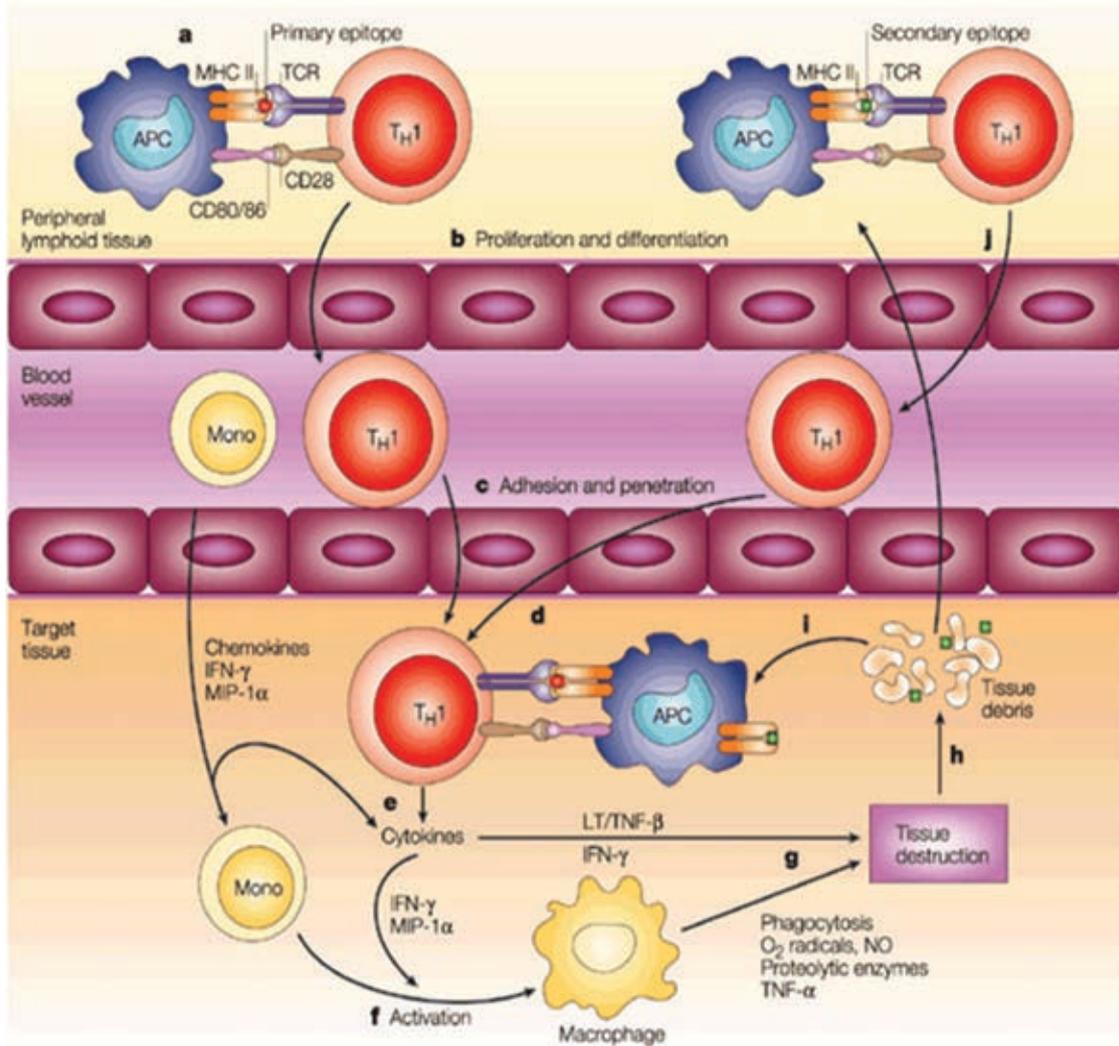
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well as additional information provided from the product prepared at the primary manufacturing facility in Seattle. APC number, APC activation, and total nucleated cells (TNC) were assessed in both the control and investigational product. Also assessed were T cell proliferation and interferon-gamma secretion by ELISPOT at treatment weeks 0, 2, and 4 in the IMPACT trial.[2,15,16] In the three trials, ex vivo APC activation was greater with sipuleucel-T relative to the control at weeks 0, 2, and 4 with the median APC activation increased approximately 6.2 fold. The median cumulative APC activation with sipuleucel-T alone across the three dose preparations was 26.7 (21.5 to 33.6). Elevated levels of T-cell activation-associated cytokines were noted during manufacture but not induced before and after exposure to GM-CSF alone. The treatment generated PA2024- and/or PAP-specific humoral responses in 68% (102/151) of patients compared with 3% (2/27) of control patients. The anti-PA2024 and anti-PAP antibody titers were greater in the

sipuleucel-T arm compared with controls at all time points post-therapy, and a persistent response detectable 26 weeks after initial post-treatment baseline. It should be noted that overall product activation was confirmed by TH_1 cytokines (IFN-gamma, TNF-alpha); TH2 cytokines (interleukin [IL]-5, IL-13) were also present implying that both TH_1 and TH_2 cells were activated in an antigen-specific manner. IL-10 was less detectable relative to those cytokines that facilitate T cell expansion such as IL-2, IFN-gamma, TNF-alpha.[12] There also appeared to be a correlation between OS and T-cell secretion of IFN-gamma by ELISPOT and PA2024-specific antibody.[12]

Can reducing or limiting the regulatory T-cell population improve the vaccine response? Apart from chemotherapy, improving vaccine response by inactivating T-regulatory (Treg) cells has been attempted through the specific targeting of the T-cell cytotoxic T-lymphocyte associated (CTLA)-4 receptor with a monoclonal antibody such as

ipilimumab.[17-19] Preliminary clinical trials suggest that administering a therapeutic vaccine followed by ipilimumab enhances immune responses and tumor reduction in prostate and ovarian cancers as well as melanoma.[20-23] In a noncomparative phase I trial (30 patients) of ipilimumab plus the PSA-TRICOM[24] vaccine in prostate cancer, OS was 31.8 months compared with an expected survival of 18.5 months based on baseline factors (Halabi nomogram–predicted survival [HPS][25]).

Fong et al[26] used microarrays spotted with more than 8,000 human proteins to assess the diversity of antibody responses modulated by treatment with CTLA-4 blockade and GM-CSF. Patients with advanced prostate cancer who had clinical responses developed robust antibody responses to a higher number of antigens than nonresponders. The antibody responses appeared to target antigens on which preexisting antibodies were likely to be present in patients who responded compared with nonresponders. Although the majority of antibody responses were patient-specific, there appeared to be a commonality of immune responses to shared antigens within the responder population. They identified one shared antigen, PAK6, which is also expressed in prostate cancer and to which CD4+ T cell responses were induced.

THE CHECKPOINT INHIBITORS: DOES ONE SIZE FIT ALL?

Although sipuleucel-T still remains an active choice for patients with asymptomatic or minimally symptomatic CRPC, the stunning and durable responses seen by the checkpoint inhibitors, ipilimumab[26-28] and nivolumab,[29,30] in prostate,[27,28] melanoma,[26,29,30] non–small cell lung,[29,30] renal,[29,30] and bladder[29,30] cancers, have provided rationale for their investigation in CRPC. The phase I/II report of a dose-escalating study of ipilimumab with and without radiation therapy to a single site in bone showed stable disease and several dramatic and durable responses. This provided the impetus for the recently reported phase III trial[28] for patients who progressed after docetaxel treatment and were randomly assigned 1:1 to receive bone-directed radiotherapy (8 Gy in one fraction) followed by either ipilimumab 10 mg/kg or placebo every 3 weeks for up to four doses. Nonprogressing patients could continue to receive ipilimumab at 10 mg/kg or placebo as maintenance therapy every 3 months until disease progression, unacceptable toxic effect, or death. This came close to, but did not meet, its endpoint of OS. An exploratory and post-hoc subgroup analysis, noted an OS benefit for ipilimumab in a subset of patients without visceral metastases, with normal or mildly elevated alkaline phosphatase, and without anemia. This suggested that ipilimumab may still be effective but in patients with more favorable prognostic features. Unlike melanoma, a highly mutated disease,[31] for which ipilimumab has been shown to have favorable effects, this has not been the case for prostate cancer. Similarly, nivolumab (anti-programmed death [PD]-1),[29,30] and its ligand (anti-PD-L1) have shown robust activity in melanoma, renal cell, non-small lung cancers, and now blad-

der cancer but minimal activity in prostate cancer. Despite this, there is still consideration to trying to maximize their effectiveness in prostate cancer via other combinatorial approaches.

DNA VACCINES

For the first time in CRPC, a phase III clinical trial of a viral-based vaccine, rilimogene galvacirepvec/rilimogene glafolivec (PROSTVAC).[32-34] Many viral-based cancer vaccines are produced via the insertion of a plasmid encoding tumor proteins (i.e., PSA, prostate-specific membrane antigen [PSMA]) into a viral vector, often a poxvirus (e.g., vaccinia, fowlpox).[35-37] After administration, host epithelial cells are infected and can, on lysis, continue to release a variety of encoded antigens that are taken up and processed by APCs for presentation to the T cell. This is accompanied by activation of CD4+ and CD8+ T cells. Alternatively, as in PROSTVAC, not only are plasmids used that encode tumor associated antigens (i.e., PSA) but there is inclusion of costimulatory molecules. In the case of PROSTVAC, three T-cell costimulatory molecules, that is, B7.1, intercellular adhesion molecule-1 (ICAM) and leukocyte function-associated antigen-3 (LFA-3) are included. As in all vaccine strategies, there are limitations especially when preclinical studies showed marked tumor regressions but the responses in man are disappointing. One shortcoming of the viral-based vaccine preparation lies in that the antibody response to vector antigens may be more exaggerated compared with the response to the plasmid encoded tumor antigens. This can induce neutralization of the vaccine with recurrent administrations.[38] PROSTVAC circumvents this by using an immunologic prime boost that by sequencing two different viruses, a vaccinia virus prime followed by a fowlpox virus boost, results in potent immune responses. Although there has been an effect on cancer cellular proliferation, the cancer cell rate of growth was also affected.[39] The authors suggest that this may provide an alternative explanation to why vaccines that yield an improved OS are not accompanied by a delayed time to progression.

A recent paper by Madan et al[40] showed that ipilimumab could be safely combined with the PSA-targeted vaccine PSA-Tricom without significantly exacerbating the agent's immune-related adverse event profile. Those patients who were chemotherapy-naive experienced a PSA decrease from baseline levels. In support of this approach, another phase I study also confirmed that ipilimumab could safely be combined with GVAX prostate.[41] Preclinical models continue to be performed to assess the translatability of these combinatorial approaches. A combination of GVAX and anti-CTLA-4 in an autochthonous prostate cancer model expressing hyaluronic acid in a prostate-restricted manner reported on the importance of timing and dosage in this kind of regimen, which may have importance in future trials with ipilimumab combinations.[42] GVAX plus anti-CTLA-4 combination therapy reduced peripheral tolerance and promoted

TABLE 1. Rationale for Combinatorial Strategies

Pros	Concerns
Although cancer cells are not highly immunogenic, therapeutic vaccines containing tumor-associated antigens plus costimulatory molecules have been found to elicit substantial immune responses.	Repeated rounds of chemotherapy at maximum-tolerated doses can reduce tumor burden and suppress, rather than enhance, immunologic efficacy.
Metastatic tumors develop highly sophisticated strategies for derailing immune defenses. Therapeutic vaccines, therefore, need support that sets the tumors back and/or resets the immune system.	Patients status post standard chemotherapy have resistant tumor cells, a shorter survival, and more suppressed immune systems. This population may not be optimal for evaluation of a novel vaccine.
Chemotherapy, if not myeloablative, has immunomodulatory effects that help restore antitumor immunity while affecting the tumor microenvironment.	Timing of chemotherapy relative to therapeutic immunization may be a critical factor in the success of a combination regimen. Is chemotherapy being used to debulk tumor burden or to improve synergism with the therapy?
Moving forward, optimization of the effectiveness of vaccine/chemotherapy regimens requires the development of clear endpoints that include biomarkers that reflect the effect of the therapy on the biology of the disease.	Basic questions remain unanswered, including the dose and timing of chemo-therapy when used in conjunction with therapeutic vaccines. It is unclear how to design trials with viable endpoints for patients with biochemical relapse or nonmetastatic castration-resistant disease.

the activation and proliferation of tumor antigen-specific CD8 T cells.

BUILDING ON IMMUNOTHERAPY—ROLE OF BIOLOGICS AND/OR CYTOTOXIC AGENTS

There have been numerous reports touting the role of chemotherapy given before an immunotherapeutic agent particularly as it pertains to reducing the Treg cell population and making the immune milieu more sensitive to immune modulation. There are three basic unknowns with respect to chemotherapy administered with an immunotherapy: identifying the optimum chemotherapy, the maximum tolerated dose, and in which sequence the agents be given (Table 1). Chemotherapeutics of interest, with an ongoing body of preclinical and early human data, notably include taxanes, anthracyclines, and cyclophosphamide, which seem to offer some positive immune modulation that might enhance the response to a therapeutic vaccine. Chemotherapy could be administered at standard or maximum-tolerated doses if the purpose is to kill the most malignant cells, or trigger lymphopenia and reset immune homeostasis. As discussed, lower-than-therapeutic doses may be favored, as those may selectively alter cell populations and inhibit angiogenesis.[43] Higher doses set the tumor back further, allowing greater immune activity and more antigenicity because of tumor debulking and cell death.[44] Lower doses and/or abbreviated courses would be less toxic overall, and also less immunosuppressive. They would also allow frequent, even daily, dosing (metronomic administration) for a steady effect over time. Induction of tumor resistance to chemotherapy, including multidrug resistance, is a possibility when giving suboptimal drug doses.[45-47] The vaccine, possibly enhanced by the chemotherapy, might provide a barrier against tumor escape. Metronomic taxanes and other agents have supplemental antiangiogenic effects as well.[45,48]

Sequencing of chemotherapy, like dosing, depends on the agent's mechanism of action. Initiation of chemotherapy before vaccination would be an option if the goal was to reset the immune system by reducing the level of suppressive cells.

On the contrary, initiation of chemotherapy during or after vaccination would be an option if the strategy was to impede the tumor and potentiate or broaden the vaccine-induced responses.

The question of which patient, clinical state, and treatment history is most appropriate for therapeutic vaccine schemes also arises. Patients with late-stage disease may have had their immune systems compromised by extensive chemotherapy and the evolving tumor escape strategies.[49-52] One implication is that the patients with shorter life expectancies will not benefit from vaccine therapy, as demonstrated in the GVAX/docetaxel combination results. The original phase III trial of GVAX compared with docetaxel enrolled patients with less-advanced disease.[53] A trend toward superior survival in the GVAX recipients after 22 months follow-up was already emerging. In another vaccine example, in a phase II study of PSA-TRICOM (32 patients), patients with HPS of 18 months or longer lived significantly longer than expected (p = 0.035).[53] Median survival was 14.6 months for patients with HPS less than 18 months and was 37.3 months or longer for those patients with an HPS of 18 months or longer.[53] Considering the safety of vaccines relative to standard chemotherapy, clinical trials could justify enrolling patients in earlier stages of disease in lieu of conventional chemotherapy alone.

T-CELL STRATEGIES: CHIMERIC ANTIGEN RECEPTOR-MODIFIED T CELLS

The genetic engineering of T cells is a novel strategy designed to accelerate the generation of tumor-specific T cells and remedy the biologic limitations that constrain the antitumoral functions of normal T cells.[54-57] Unlike the physiologic T-cell antigen receptor (TCR), chimeric antigen receptors (CARs) encompass immunoglobulin variable regions or receptor ligands as antigen-recognition elements, thus, permitting T cells to recognize cell surface tumor antigens in the absence of HLA expression (Fig. 1). T-cell activation is mediated by the cytoplasmic domain of the CAR, which is typically derived from the CD3-zeta chain or the FcRI-gamma

TABLE 2. Target Molecules and Their Respective Constructs Used in Preclinical/Clinical Trials

Antigen	Malignancy	Receptor Type
CD19, 20	B-cell malignancies	scFv-CD3zeta
PSMA	Tumor neovasculature	scFv-CD3zeta
PSCA	Pan-carcinoma	Under study
ERBB2	Breast and others	scFv-CD28-CD3zeta
GD$_2$	Neuroblastoma	scFv-CD3zeta, scFv-CD28
MDM2	Pan-carcinomas	alpha beta TCR
CEA	Colorectal cancer	scFv-CD28-CD3zeta
VEGF-R2	Tumor neovasculature	scFv-CD3zeta
KDR	Tumor neovasculature	scFv-Fc xi Rl gamma
EGP2	Colorectal cancer	scFv-CD3zeta, scFv-Fc xi Rl gamma

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chain (Table 2, Figs. 2 and 3). Our group has shown that the zeta chain–based CARs could induce strong activation capable of sustaining T-cell proliferation and permitting secondary antigenic restimulation in vitro provided that antigen was presented in the context of CD28-mediated costimulation.[54,58,59] In an effort to determine if T cells—particularly human T cells—expanded in this manner could mediate tumor eradication in vivo and if further in vivo costimulation would be needed to sustain their function, three tumors models using severe combined immunodeficiency-beige/beige mice were developed that showed that PSMA-targeted T cells could effectively eliminate prostate cancer. T cells were transduced with Pz1, a CAR-targeting human PSMA.[60,61] The Pz1 receptor encompasses the zeta chain of the CD3 complex as its activation domain and specifically redirects in vitro cytolysis again PSMA-positive tumor cells lines. The tumor models included orthotopic, subcutaneous, and pulmonary

diseases; tumor eradication was directly proportional to the in vivo effector-to-tumor cell ratio. Serial imaging studies revealed that the T cells had to survive for at least 1 week to induce durable remissions. The administration of Pz1-transduced T cells induced objective responses in all mice and cured a substantial fraction of them. Based on the favorable responses, several clinical trials have been actively pursuing this approach using unique combinations with constructs that encompass unique vectors or are given in combination with cytokines. Although these approaches have been well-tolerated—stable disease has been seen but in a majority of cases—a cytokine release syndrome is observed following administration of the cells suggesting T cell activation.[62,63] Achievement of maximal responses in solid tumor may depend on the nature of the vector, the ability of cells to migrate to and persist at the tumor site, incorporation of a multiantigen construct with molecules such as PSA, PAP, PSMA, or prostate stem cell antigen or delivering a sufficient number of cells to reach the tumor site without causing worsening toxicities.

HEREIN LIES THE FUTURE

Although prostate cancer is a suitable target for immunotherapy given the variety of prostate cell surface antigens that can serve as immune targets, the availability of a serum biomarker, that is, PSA, and the fact that immunotherapy is a reasonable treatment for all clinical states of the disease, how to build on current therapies remains a challenge. Alternative strategies include OX40 and its ligand OX40L, which are members of the tumor necrosis factor (TNF) superfamily and can augment T-cell expansion, cytokine production, and survival. OX40 signaling also controls regulatory T cell differentiation and suppressive function. OX40 agonists have

FIGURE 2. Structure of Physiologic Antigen Receptors
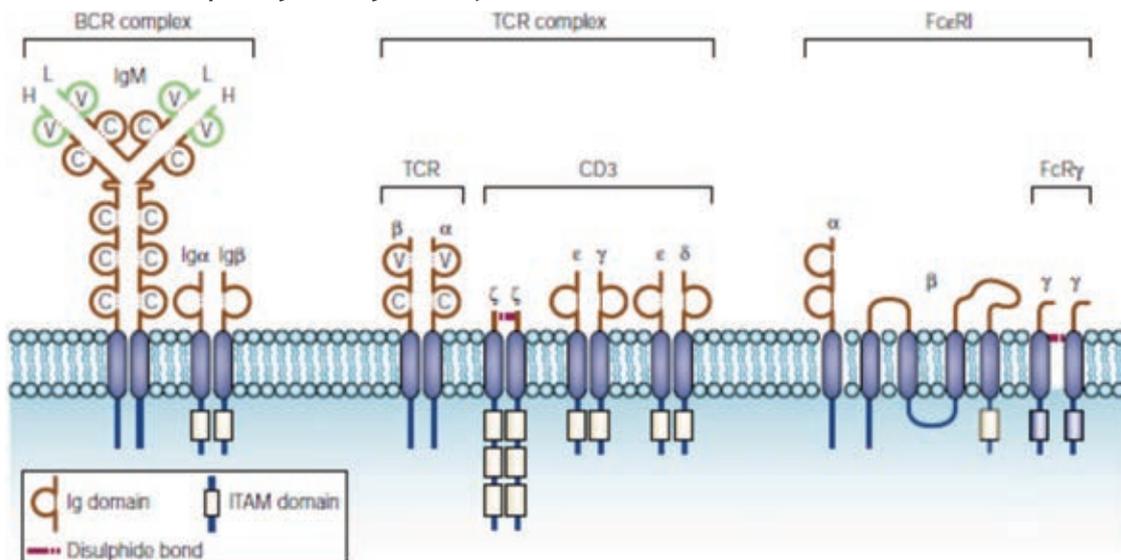
Reproduced with permission of publisher.[54]

FIGURE 3. Examples of Chimeric Antigen Receptors[54]
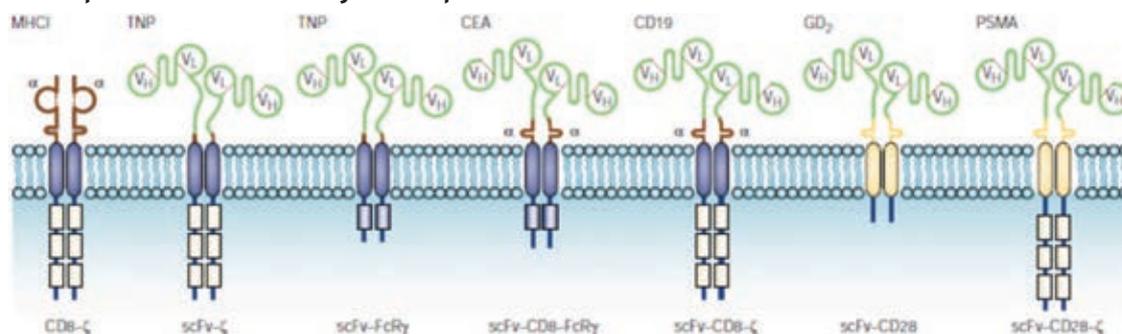
Many chimeric antigen receptors (CARs) interact with antigen through ScFvs–the antigen binding regions of immunoglobin that consist of rearranged Heavy (VH) and light VL chains linked by a short peptide linker. The CD8/zeta fusion receptor engages HLA class I molecules. Other CARS specifically bind trinitrophenol (TNP), carcinoembryonic antigen (CEA), CD 19, G_{D2} ganglioside, and prostate specific membrane antigen (PSMA). They incorporate various portions of the B-cell antigen receptor (light green), T-cell receptor-CD3 complex (ivory), CD8alpha (brown), FcRgamma (blue ITAM domains), and CD28 (yellow) cytoplasmic activation domains (blue ovals). The P28 zeta receptor, which recognizes PSMA, includes signaling domains from both CD28 and CD3 zeta. Reproduced with permission of publisher.[54]

been shown to enhance antitumor immunity in preclinical models using immunogenic tumors.[64] A recent phase I trial in patients with metastatic castration- and chemotherapy-resistant prostate cancer evaluated the toxicity and the effect of cyclophosphamide combined with radiotherapy and an anti-OX40 agonist on peripheral blood lymphocytes (PBLs).[65] There was no effect of the combination on the degree of proliferation of PBLs. There was no change in the proliferation of CD4+ FoxP3+ T cells (Treg), but there was a trend toward a higher percentage of cycling CD8+ T cells expressing activation markers CD38 and HLA-DR. OX40 and its ligand remain interesting targets for future development.

Clinical trials in the castration-resistant nonmetastatic state evaluating combinations of the antiandrogen flutamide with or without the addition of PROSTVAC/PSA-TRICOM in delaying disease progression are ongoing [NCT00450463]. Another randomized phase II trial is examining the combination of PROSTVAC/TRICOM and the AR-directed agent enzalutamide to determine if the combination will increase time to progression (as defined by Prostate Cancer Clinical Trials Working Group 2 criteria [NCT01867333]). The results of the phase III multinational randomized trial of PROSTVAC in patients with asymptomatic of minimally symptomatic CRPC are eagerly awaited. This 800-patient trial has reached its target accrual and is comparing the OS and proportion of patients who remain event-free (radiological or pain progression, initiation of chemotherapy, or death) at 6 months.

CONCLUSION

The mix and match approach—that is, combining immunologic agents with different mechanisms of action or even within the same class[66]—supports the rationale for continuing research in immunotherapy for prostate cancer. While understanding mechanistically how antitumor effects may occur,[67] it is important to keep in mind that the manner in which a therapy induces an antitumor response may be unclear, and as such should not deter investigators from using the drug.

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Evolving Immunotherapy Strategies in Urothelial Cancer

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OVERVIEW

The treatment of nonmuscle-invasive urothelial carcinoma with bacillus Calmette-Guérin (BCG) represents the importance of immunotherapy in the treatment of cancer. Despite its clinical efficacy, up to 30% of patients will ultimately experience progression to muscle-invasive disease. This, along with an improved understanding of the biologic pathways involved, has led to efforts to improve, enhance, or alter the immune response in the treatment of urothelial carcinoma. A number of novel therapeutic approaches currently are being pursued, including recombinant BCG to induce T helper type 1 (Th1) immune responses, nonlive *Mycobacterium* agents, targeted agents toward cancer-associated antigens, immune-modulating vaccines, and adoptive T-cell therapies. Here, we review the current and future immunotherapy treatment options for patients with urothelial cancer.

In 2013, cancer immunotherapy was declared the breakthrough of the year by *Science* magazine.[1] Since then, there has been a frenetic dash toward the development and implementation of immune-based therapies in all cancers, including urothelial cancer. However, immunotherapy has a long and successful history in the treatment of bladder cancer, with BCG intravesical immunotherapy as the leading therapy for nonmuscle-invasive bladder cancer (NMIBC). We will review the current and future immunotherapy treatment options for patients with urothelial cancer.

BCG

BCG is a live attenuated strain of *Mycobacterium bovis* developed initially in 1921 as a vaccine for tuberculosis. In 1976, Morales et al[2] reported the first successful use of intravesical BCG therapy in the treatment of recurrent superficial bladder cancer. It has been demonstrated to reduce recurrence rates and progression to muscle-invasive disease in patients with carcinoma in situ (CIS) and with superficial bladder tumors.[3-5] BCG has gone on to become the standard of care in the treatment of high-grade NMIBC after transurethral resection.

Although BCG has been a mainstay treatment of NMIBC for more than 3 decades, the exact mechanism by which BCG achieves its therapeutic effect remains an area of investigation. Zbar and Rapp[6] in 1974 discovered several conditions required to obtain an antitumor effect with BCG, including the ability to develop an immune response, a sufficient number of live BCG, close contact between BCG and cancer cells, and a low tumor burden.

As early as 1959, it was recognized that the antitumor effect of BCG was mediated through the activation of an immune response and induction of the inflammatory response.[7] Additional studies have confirmed that an intact immune system, particularly the cellular system, is required for achievement of a therapeutic response. Abundant evidence indicates that intravesical BCG results in an extensive influx of inflammatory cells and cytokine production, which results in an immune response against tumor cells.

The immune response is preceded by the attachment of BCG to urothelial cells. The normal urothelium is lined with glycosaminoglycans (GAGs), which have been suggested as a primary defense mechanism against noxious elements in urine.[8] The antibacterial properties of GAGs are secondary to its hydrophilic, highly negative charge, imposing a barrier between the urothelium and urine. After instillation into the bladder, BCG adheres to urothelial cells via fibronectin, a glycoprotein that is part of the extracellular matrix. BCG attaches to fibronectin through its fibronectin attachment protein. The importance of this interaction has been demonstrated in a mouse model, in which blocking fibronectin attachment reduced the delayed-type hypersensitivity response and antitumor activity.[9] Internalization of BCG by urothelial, tumor, and inflammatory cells triggers an inflammatory cascade of cytokine release and immune cell recruitment. This results in an influx of granulocytes, macrophages, natural killer cells, dendritic cells, and lymphocytes. Many studies have examined the cytokines present in the urine of patients treated with BCG and found elevated amounts of interleukin (IL)-1, IL-2, IL-6, IL-8, tumor necrosis factor (TNF)–alpha, interferon (IFN)-gamma, and granulocyte-macrophage colony-stimulating factor (GM-CSF).[10,11] In addition, an anti-BCG–specific immune response via antigen

presentation to T cells amplifies the response. Ratliff et al[12] showed that the absence of either CD4 or CD8 T-cell subsets eliminated the BCG-mediated antitumor activity.

Although BCG is a very effective intravesical treatment for high-grade NMIBC, ultimately 20% to 50% of patients will experience recurrence after a successful induction cycle.[13] Of these patients, 25% to 45% can benefit from salvage therapy with a second induction course.[14] Side effects of intravesical BCG are common. A randomized EORTC trial assessed the dose and duration of maintenance BCG in patients with intermediate- and high-risk NMIBC.[15] Of the 1,316 patients enrolled, 62.8% reported local side effects and 30.6% reported systemic side effects. The most frequent local and systemic side effects reported were chemical cystitis in 35% of patients and general malaise in 15.5% of patients.

Prolonged BCG treatment is limited in some patients by the development of severe local side effects and/or recurrent and/or progressive disease. Rarely, BCG systemic toxicity also can preclude further BCG use. Although radical cystectomy is an effective procedure for these patients, it can be accompanied by considerable morbidity and an altered quality of life.

RECOMBINANT BCG

Recombinant BCG (rBCG) options have been engineered to address the stated limitations of BCG. rBCG consists either of Th1 cytokine-secreting rBCG strains or of non-live rBCG strains that contain BCG subcomponents (see Table 1).

TH1 CYTOKINE-SECRETING RBCG

The most common Th1 cytokines incorporated into rBCG strains include IL-2, IL-12, IL-18, IFN-alfa, and IFN-gamma.[16] In vitro, IL-2 enhances the production of cytotoxic lymphocytes and the cytotoxic activity of natural killer cells and monocytes.[17] In patients treated with BCG, increased IL-2 levels are noted in the urine shortly after BCG adminis-

KEY POINTS

- Bacillus Calmette-Guérin (BCG) represents one of the most successful applications of immunotherapy and currently is the most effective treatment for high-grade nonmuscle-invasive bladder cancer.
- Recombinant BCG may enhance the cytotoxic T-cell response required for BCG-mediated antitumor effects while reducing local side effects.
- Checkpoint blockade inhibitors are a novel class of immunotherapeutics agents that target and interfere with immune stop signals.
- Vaccines present the opportunity for long-term success and are the ultimate goal.
- Adoptive T-cell immunotherapy can induce rapid immunity but carries the risk of off-target toxicities.

TABLE 1. Targeted Therapies

Agent	Target(s)
rBCG	
Th1, cytokine secreting	IL-2, IL-12, IL-18, IL-α, IL-γ
BCG, subcomponent based	Mycobacterial cell wall, BCG cell wall
Monoclonal Antibodies	
Checkpoint blockade inhibitors	CTLA-4, PD-L1
Tumor-associated antigens (CDX-1307)	β-HCG
Vaccine	
AdHER2 dendritic cell vaccine	HER2/neu
CTAs	NY-ESO-1, recMAGE-A3
PANVAC	MUC-1, CEA
Adoptive T-cell Therapy	
TIL	CTAs (eg, NY-ESO-1)
CART	TAA

Abbreviations: rBCG, recombinant bacillus Camille-Guerin; Th1, T helper cell 1; IL, interleukin; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-L1, programmed death ligand 1; HCG, human chorionic gonadotropin; CTA, cancer testis antigen; TIL, tumor-infiltrating lymphocyte; CART, chimeric antigen receptor T cell; TAA, tumor-associated antigen.

tration.[18] Therefore, IL-2 rBCG strains have been engineered and studied in animal models: IL-2 rBCG strains induce a more favorable ratio of IFN-gamma to IL-4,[19] accelerate greater antigen-specific proliferation,[20] and release more Th1 cytokines than BCG.[20] IL-12 has a very complementary function to IL-2 and has been shown to induce tumor regression and improve survival in animal models as a single agent.[21] Our colleagues at the National Cancer Institute (NCI) showed that intravesical IL-12 can be more successful than intravesical BCG in treating orthotopic murine tumors when it is combined with chitosan.[22] Furthermore, its role in immunotherapy is vital, because IL-12 knockout (and IFN-gamma knockout) mice do not respond to BCG therapy.[23] Unfortunately, a phase I trial of intravesical recombinant IL-12 demonstrated no activity in patients[24] (although the IL-12 in this trial was not combined with chitosan); to date, no trial results with IL-12– based rBCG are available. IL-18 is secreted from activated macrophages and, similar to IL-2 and IL-12, can synergize BCG activity by inducing Th1 cytokines.[25] In vitro, IL-18 – based rBCG enhances macrophage cytotoxicity and cellular proliferation of IFN-gamma–secreting cells.[26]

Unlike the previous cytokines, IFN-alfa has been widely used in patients, often in conjunction with BCG. Preclinical work demonstrates that IFN-alfa can induce apoptosis by increased TNF–related apoptosis-inducing ligand (TRAIL) expression[27] and reduced angiogenesis in bladder tumors.[28] Although a large, phase II trial showed the efficacy and tolerability of BCG given with IFN-alfa, it is unknown whether the combination offers any benefit compared with BCG monotherapy.[29] The IFN-alfa–secreting rBCG strain is superior to BCG in the production of IFN-gamma from peripheral blood mononuclear cells (PBMCs) and in the enhancement of PMBC cytotoxicity toward bladder cancer cells.[30,31] IFN-

gamma is an essential cytokine for BCG efficacy, and it has been shown to reduce proliferation in bladder cancer cell lines.[23,32] In a murine model, IFN-gamma–based rBCG up-regulated major histocompatibility complex (MHC) class I molecules on murine bladder cancer cells and, compared with the control rBCG strain, increased CD4^{+} T cells, IL-2, and IL-4 in the bladder and prolonged survival after intravesical administration.[33]

BCG SUBCOMPONENT-BASED RBCG

Most of the evaluated subcomponents are portions of the BCG cell wall. Mycobacterial cell wall extract demonstrated excellent activity: 41.1% of patients had negative cystoscopies and biopsies at 60 weeks after therapy.[34] However, it contained thimerosal, a known organomercurial preservative with the potential for neurotoxicity. A newer formulation without thimerosal, called mycobacterial cell wall complex (MCC), was subsequently evaluated in a multicenter study in 2009. Fifty-five patients (82% of whom had previously experienced treatment failure with BCG) received MCC induction and maintenance at two different doses. At 26 weeks of follow-up time, the complete response rates were 27.3% in the 4-mg group and 46.4% in the 8-mg group.[35] Unfortunately, a phase III trial (NCT01200992) comparing MCC with mitomycin C in patients with BCG–recurrent/refractory bladder cancer closed early because of poor accrual. Finally, the BCG cell wall skeleton has been studied further after being incorporated into other particles, because it has unfavorable characteristics for penetration of the urothelium by itself. Both a liposomal and a lipid nanoparticle formulation have demonstrated antineoplastic effects in animal models.[36,37]

MONOCLONAL ANTIBODIES

Most excitement in immunotherapy is focused on monoclonal antibodies directed against tumor-associated antigens (e.g., beta-HCG, cytotoxic T-lymphocyte–associated antigen 4 [CTLA-4], programmed death ligand 1 [PD-L1]). Beta-HCG is expressed in 35% to 75% of bladder cancers, and expression correlates with a worse prognosis.[38] CDX-1307 is an interesting monoclonal antibody that functions like a vaccine in the body. It consists of the beta-HCG subunit genetically fused to the human monoclonal antibody B11 that is specific for the mannose receptor on antigen-presenting cells (APCs). On administration, CDX-1307 is internalized by APCs and, in processing, presents beta-HCG as an antigen to CD4^{+} and CD8^{+} T cells.[39] Thus, it has been proposed as a therapy in beta-HCG– expressing bladder cancers.

Checkpoint blockade inhibitors are extremely popular now, because they target inhibitors of the immune response. T cells engage APCs via their T-cell receptor as the primary signal; however, a secondary costimulatory signal is provided by CD28 (on the T cell) and B7 (on the APC). To prevent excessive T-cell proliferation, an inhibitory signal, CTLA-4, can be expressed by activated T cells and competes with CD28 in binding to B7 on APCs. This can mitigate a T-cell response in a normal circumstance. However, in cancer, T-regulatory cells (Tregs) are expressed in the tumor microenvironment and can constitutively express CTLA-4, which can suppress an anticancer immune response.[40] Therefore, CTLA-4–blocking antibodies have been developed as a therapeutic strategy. These antibodies have prolonged overall survival in metastatic melanoma but cause grade 3 or 4 toxicities in the 10% to 15% range.[41] A pilot presurgical trial in patients with urothelial cancer demonstrated that peripheral and tumor CD4 T cells had increased expression of inducible costimulator (ICOS) in response to an anti–CTLA-4 antibody. These CD4^{+} ICOS (hi) T cells produced IFN-gamma, recognized NY-ESO-1 as a tumor antigen, and increased the ratio of effector T cells to Tregs.[42] A subsequent phase I trial of 12 patients with urothelial cancer demonstrated only grades 1 to 2 toxicities, and all patients expressed CD4^{+} ICOS (hi) T cells in tumor tissues and systemic circulation. These preliminary findings with the use of CTLA-4–blocking antibodies have stimulated efforts to evaluate the efficacy of these antibodies in urothelial cancer.

As an immune response progresses, CD4 and CD8 T lymphocytes will upregulate the expression of other checkpoint inhibitors, such as the programmed death 1 (PD-1) receptor. Inflammatory conditions will prompt IFN release, which will upregulate PD-L1 and PD-L2 in peripheral tissues to maintain immune tolerance and prevent autoimmunity. Binding of PD-L1 and/or PD-L2 to PD-1 results in dephosphorylation of proximal signaling molecules downstream of the T-cell receptor complex via *src* homology region 2 domain–containing phosphatase (SHP)-1 and SHP-2 as well as augmentation of phosphatase and tensin homolog (PTEN), leading to decreased T-cell proliferation, survival, and protein synthesis.[43] However, many cancers take advantage of this checkpoint blockade by upregulating PD-L1 expression on their surface, and urothelial cancers have higher levels of PD-L1 relative to other tumors.[44] Among urothelial tumors, PD-L1 expression is higher among BCG treatment failures[45] and among more aggressive and metastatic tumors.[46]

The PD-L1 expression data would suggest activity in metastatic tumors with a PD-L1 blockade. A recently completed phase I clinical trial evaluated the anti–PD-L1 monoclonal antibody, MPDL3280A, in patients with metastatic urothelial bladder cancer.[47] This antibody has an Fc domain modification that prevents antibody-dependent cellular cytotoxicity so that local T cells were not killed and thereby depleted. As a result, the antibody inhibits the interaction of PD-L1 with PD-1. In this trial, 72% of the patients experienced failure of two or more prior systemic regimens. The overall objective response rate (ORR) for all 65 patients was 26%. However, the ORR varied on the basis of the degree of immunohistochemistry (IHC) staining of tumor-infiltrating cells or tumor cells. Strong (2+ to 3+) PD-L1 expression by IHC (5% or greater PD-L1 positive) resulted in a 43% ORR, whereas weak (0 to 1+) PD-L1 expression by IHC (less than 5% PD-L1 positive) resulted in an 11% ORR.

The median time to first response was 42 days, and the median overall survival times were 4.2 months for the strong IHC expression group and 2.7 months for the weak IHC expression group. Importantly, the main toxicity of the therapy was fatigue, and grade 3 adverse events only occurred in 4% of patients (no grade 4 or 5 toxicity noted). On the basis of the encouraging results of this trial, the U.S. Food and Drug Administration (FDA) granted MPDL3280A a breakthrough designation in June 2014.

VACCINES

HER2 status has prognostic and therapeutic value in breast cancer. Recently reported results from The Cancer Genome Atlas[48] found that HER2 alterations were almost as frequent in urothelial carcinoma compared to the TCGA breast cancer study. A meta-analysis of nine retrospective studies (2,242 patients) indicated that HER2 expression significantly correlated with poorer disease-specific survival (hazard ratio [HR] 2; 95% CI, 1.22 to 3.29; p = 0.006) and disease-free survival (HR 1.68; 95% CI, 1.33 to 2.14; p < 0.0001) of patients with bladder cancer.[49] DN24–02 is an investigational active cellular immunotherapy targeted at the HER2 receptor. It consists of autologous PBMCs, including APCs, which are activated ex vivo with a recombinant fusion protein. A randomized phase II study comparing adjuvant DN24–02 to the standard of care in patients with high-risk urothelial cell carcinoma met accrual and results are pending at this time. Colleagues at the National Institutes of Health Clinical Center are investigating the use of another HER2/*neu* vaccine in a phase I trial (NCT01730118). This trial investigates a novel therapeutic autologous AdHER2 dendritic cell vaccine in patients with HER2-expressing metastatic solid tumors as well as in patients with adjuvant bladder cancer who have HER2-positive tumors. In preclinical animal models, the vaccine was documented to eradicate large established tumors through the induction of polyclonal, anti-HER2 antibodies.

M phase phosphoprotein 1 and disheveled, EGL-10, and pleckstrin (DEP) domain have roles in the growth of bladder cancer cells. In addition, human leukocyte antigen (HLA)-A24–restricted peptide epitopes corresponding to parts of these two proteins have been identified that can induce peptide-specific cytotoxic T cells. Of the six patients with metastatic bladder cancer enrolled in a phase I trial, four developed vaccine-specific cytotoxic T cells.[50]

Cancer testis antigens (CTAs) are a group of tumor-associated antigens with restricted expression in normal tissues but with expression in a variety of tumors. Sharma et al[51] examined the expression patterns of nine CTA by IHC and reverse transcriptase (RT) polymerase chain reaction (PCR) in a panel of 95 high-grade bladder tumors. They found that at least one CTA was expressed in 77% of the tumors and that 61% of the tumors expressed more than one. A recombinant NY-ESO-1 protein vaccine coadministered with GM-CSF and BCG as immunologic adjuvant was tested in six patients with organ-confined disease.[52] NY-ESO-1–specific antibody responses were induced in five patients, CD8 T-cell responses occurred in one patient, and CD4 T-cell responses were seen in all six patients. A phase II trial (NCT01435356) evaluating the efficacy of the recMAGE-A3 vaccine after cystectomy is currently recruiting; a phase I trial (NCT01498172) evaluating MAGE-A3 plus BCG has just completed, and results are pending.

PANVAC is a poxviral cancer vaccine that has demonstrated therapeutic efficacy against a variety of carcinomas. PANVAC consists of a primary vaccination with a replication-competent recombinant vaccinia vector followed by multiple boosts with a replication-incompetent recombinant fowlpox vector. These vectors contain transgenes for both human T-cell costimulatory molecules and tumor-associated antigens against Mucin-1 (MUC-1)[53,54] and carcinoembryonic antigen (CEA).[55] MUC-1 and CEA are expressed in approximately 93% and 76% of high-grade bladder tumors, respectively. A phase II study (NCT02015104) assessing PANVAC in combination with intravesical BCG in patients who have experience treatment failure with prior BCG therapy is recruiting patients at the NCI and the Rutgers Cancer Institute of New Jersey.

ADOPTIVE T-CELL THERAPY

Adoptive T-cell therapy involves the infusion of externally manipulated T cells to give rapid immunity instead of relying on the immune system to generate T cells after being presented with an antigen. Before infusion, however, patients require nonmyeloablative leukoreductive therapy using irradiation and chemotherapy.[56] This area of cancer immunotherapy began with tumor-infiltrating lymphocytes (TILs). These TILs are extracted from tumor tissue, expanded ex vivo, and then reinfused into patients. This approach was applied recently to patients with metastatic urothelial cancer in a feasibility study. Tumor lymphocytes were obtained from lymph nodes draining metastatic tumors; after in vitro culture, the lymphocytes were reinfused into the patients without any adverse effects.[57] However, it is unclear how effective this approach will be. A more novel approach applies extraction of TILs from tumors and whole-exomic sequencing of the tumors to identify mutations characteristic of the tumor. The TILs are probed to see if they recognize any of the mutations; then, adoptive transfer of the TILs containing mutation-specific polyfunctional T cells is performed.[58] This technology can be applied to any malignancy, and, given that urothelial cancer has the third highest rate of mutations, it is well positioned for this type of therapy. We are assisting our colleagues who are performing this work at the NCI in the application of this approach to urothelial tumors.

TIL therapy is limited in that TILs have to be retrieved through an invasive procedure and require the ability to grow ex vivo. As a result, genetic modification of the T-cell receptor (TCR) only requires isolation from peripheral blood, viral transduction to express a recombinant TCR specific for a tumor antigen, and reinfusion after expansion of these genetically engineered TCRs. CTAs, as mentioned earlier, are good candidates for TCR gene therapy, because they are not present in adult somatic tissues and are found with high

frequency in some tumors. For example, NY-ESO-1 is expressed in 80% of patients with synovial cell carcinoma patients. In a trial of patients who had metastatic synovial cell carcinoma, four of six patients achieved objective clinical responses after treatment with a TCR directed against NY-ESO-1.[59] This technology still requires the presence of the target antigen on the tumors and is restricted to patients who have certain HLA alleles. Also, if the tumor responds by MHC downregulation, then this therapy may be limited. However, this therapy seems attractive to apply toward urothelial tumors, given their high expression of CTAs.

A novel form of adoptive immunotherapy has evolved that can avoid the MHC restriction and the immune escape phenomenon that may be seen with genetically engineered TCRs. Chimeric antigen receptor T-cell therapy entails isolation of a patient's peripheral T cells and subsequent transduction by a chimeric receptor that consists of a single-chain variable region of an antibody domain (scFv) that is specific for a desired tumor-associated antigen (TAA) with a CD3/T cell. Because the antibody portion of the chimeric receptor is binding to the TAA, the binding is non-MHC restricted. The T-cell portion engages the native T-cell receptor–mediated activation on binding. Therefore, this approach combines the cytotoxicity of a

$CD8^+$ T cell with MHC-independent antigen recognition of a monoclonal antibody.[56]

CONCLUSION

Immunotherapy has become a popular approach to target tumors in the last decade. Urothelial cancer is a malignancy that has a long history of successful treatment with BCG. Despite this success, the high recurrence and progression rates of localized disease along with the dismal prognosis of metastatic disease warrant improvement in the current treatment. Recombinant BCG strategies are promising for BCG-refractory disease or for patients who cannot tolerate further BCG. Monoclonal antibodies, and specifically checkpoint blockade inhibitors, have been especially exciting and are the newest therapies for metastatic urothelial cancer. These therapies likely will be applied to localized, BCG-refractory disease also. Vaccines that target TAAs, such as HER2, CTA, and MUC-1/CEA are promising, given the high expression in urothelial cancer and the tolerability of these treatments. Finally, adoptive T-cell therapy is very promising; although this area of immunotherapy has not been explored fully in urothelial cancer, the high rate of mutations in urothelial cancer and the prevalence of urothelial-specific TAAs make this a promising area of future research.

Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

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Emerging Role for Novel Immunotherapy Agents in Metastatic Renal Cell Carcinoma: From Bench to Bedside

Matthew Weinstock, MD, and David F. McDermott, MD

OVERVIEW

Therapies that augment the antitumor immune response have been an established treatment modality for metastatic renal cell carcinoma (mRCC) since the 1980s. An improved understanding of the factors that limit the immune response to cancer have led to the development of novel therapeutic agents. Most notably, monoclonal antibodies that block the programmed death (PD)-1 immune checkpoint pathway have demonstrated encouraging antitumor activity against mRCC in phase I and II clinical trials. However, as monotherapy these agents are unlikely to offer substantial clinical benefit for the majority of patients with mRCC. Combination approaches and improvements in patient selection will be essential to enhance their efficacy and ensure the rational application of immunotherapy. This review summarizes the clinical and preclinical data that support the use of novel immunotherapies for mRCC and looks forward to future directions for this promising therapeutic strategy.

Cytokine-based immunotherapies, such as interferon-alfa and interleukin (IL)-2, have been used for the treatment of mRCC since the 1980s.[1-9] Although some patients experience a dramatic benefit with this approach, a majority fail to achieve long-term disease-free intervals. Substantial improvements in the outcomes of patients with mRCC have occurred over the past decade with the development of therapies targeting the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways,[10-22] but mRCC continues to account for an estimated 13,860 deaths per year in the United States.[23] Identifying therapeutic strategies that promote durable remission of metastatic disease remains critically important.

Conventional immunotherapies often fail to provide long-term control of cancers because neoplasms are able to evade immune-mediated attack through several mechanisms. These include: (1) preferential proliferation of T regulatory cells (Tregs), which leads to decreased acute inflammation, (2) increased intratumoral levels of immunosuppressive cytokines, such as interleukin (IL)-6, TGF-beta, and IL-10, (3) increased expression of immune checkpoint modulators that serve to limit the inflammatory response, and (4) poor trafficking of immune effector cells to the tumor itself.[24-26] Gajewski et al have described two distinct tumor phenotypes as a model to conceptualize these different mechanisms of resistance to immune-mediated destruction: a "noninflamed phenotype" in which tumors have low levels of chemokine production and lymphocyte infiltration (and therefore might benefit from therapies designed to increase lymphocyte traf-

ficking to tumors, such as tumor vaccination); and an "inflamed phenotype" in which tumors have rich chemokine levels and variable T-cell infiltration, but also contain increased levels of immunosuppressive Tregs and immune checkpoint modulators (and therefore might benefit from therapies designed to inhibit Tregs or immune checkpoint molecules).[26]

Although there is evidence that immunotherapy can be an effective therapeutic modality for mRCC, further efforts are needed to take full advantage of this approach for both tumors that display the inflamed phenotype and tumors that have the noninflamed phenotype. Novel immunotherapy strategies, including immune checkpoint inhibitors, suppressors of Tregs, T-cell agonists, and tumor vaccines, and combinations of these various modalities with FDA-approved therapies, have produced interesting preliminary data in ongoing clinical trials.

NOVEL IMMUNOTHERAPY FOR MRCC: A BRIEF SUMMARY OF THE ROLE OF IMMUNE CHECKPOINT INHIBITION

Interactions between molecules on the surfaces of T cells and antigen-presenting cells at the immune checkpoint can lead to the induction of immune tolerance. The most clinically relevant of these interactions are those between cytotoxic T lymphocyte associated protein-4 (CTLA-4) on T cells and its ligands B7-1 and B7-2 on antigen-presenting cells, and those between PD-1 on T cells and its main ligand PD-L1 on

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antigen-presenting cells or tumor cells. It has been noted that mRCC tumor cells themselves can also express PD-L1 and thereby activate the immunoregulatory function of the PD-1/PD-L1 interaction to create an immunosuppressive tumor microenvironment.[27] Monoclonal antibodies that inhibit the negative immune regulators present in inflamed tumors lead to upregulation of antitumor immune function and have demonstrated potent effects in both laboratory and clinical studies of various malignancies, including mRCC.[28-39]

Nivolumab, a fully human monoclonal IgG4 antibody specific for human PD-1, demonstrated an objective response rate of 29% in a phase I trial and 21% in a phase II clinical trial of patients with mRCC who had failed standard therapy.[40-42] Blockade of PD-L1, the primary ligand for PD-1, with MPDL3280A yielded an overall response rate of 15% in a phase I cohort of patients with mRCC.[43-44] Additionally, a substantial number of patients in these early clinical trials experienced stable disease for longer than 24 weeks. Whether this level of antitumor activity will translate into prolonged overall survival remains the crucial question for phase III trials. A randomized trial of nivolumab versus everolimus (known as CheckMate 025) completed enrollment in February 2014, with results forthcoming.[45]

The antitumor activity produced by these agents indicates that the majority of patients with metastatic RCC will not experience durable improvement with PD-1/PD-L1 blockade as monotherapy, particularly once the treatment is stopped. Ongoing investigation will focus on improving antitumor activity, particularly in noninflamed tumors, by combining PD-1/PD-L1 blockade with other immunomodulatory agents.

FUTURE DIRECTIONS OF IMMUNOTHERAPY IN MRCC
Combinations of PD-1/PD-L1 Blockade and Other Immune Checkpoint Inhibitors or Angiogenesis Inhibitors

Combinations of PD-1/PD-L1 blockade and either angiogenesis inhibitors or other immune checkpoint inhibitors

may lead to improved antitumor effects compared to inhibition of either pathway alone.[46-52] Preliminary results of phase I clinical trials of these combinations have demonstrated encouraging response rates (e.g., 43 to 48% with nivolumab/ipilimumab and 52% with nivolumab/sunitinib) at the expense of markedly increased rates of toxicity.[53-54] Several other phase I trials of different combinations are currently under investigation (Table 1).[55-64] Randomized phase III studies will be necessary to better define the optimal combination of these agents and their proper sequence in relation to standard approaches.[65]

T-Cell Agonists

Therapies that increase T-cell activity, including IL-2, CD137 agonist antibodies, and interleukin-21 (IL-21), may improve the effectiveness of immune checkpoint inhibitors.[66] CD137 (also known as 4–1BB), which serves as a costimulatory molecule for T cells and leads to increased cytokine production, effector cytolytic activity, and T-cell survival, has been demonstrated to eradicate mRCC in murine models.[67-73] A phase IB clinical trial of a CD137 agonist monoclonal antibody (PF-05082566) in combination with anti–PD-1 therapy in humans with advanced solid malignancies is currently ongoing.[74]

The cytokine IL-21 is produced by activated $CD4^+$ T helper cells and has been demonstrated to increase the density of $CD8^+$ T cells in murine models of both melanoma and mRCC and lead to antitumor responses against these malignancies when administered to mice.[75-76] A phase I clinical trial of intravenous recombinant IL-21 in metastatic RCC demonstrated partial responses in 4 of 19 patients, with a tolerable toxicity profile.[77] Although a subsequent phase I trial of recombinant IL-21 in combination with sunitinib demonstrated dose-limiting hematologic toxicities,[78] a phase I/II trial of IL-21 and sorafenib revealed an acceptable toxicity profile with a response rate of 21%.[79] A trial of IL-21 and PD-1 blockade might therefore be a rational combination to test in mRCC.

Elimination of Tregs

Tregs are a subpopulation of $CD4^+CD25^+FOXP3^+$ T cells that serve an immunosuppressive function.[80-82] Therapeutic agents that deplete or eliminate Tregs, such as monoclonal antibodies against chemokine receptor 4 (CCR4) or CD25, or the cytokine–toxin conjugate denileukin diftitox, could therefore augment the immune response to malignancies.

CCR4 is expressed selectively on Tregs among immune cells, and also on some tumor cells themselves. In preclinical studies, blockade of CCR4 with monoclonal antibodies decreased the level of Tregs and induced T-cell responses specific to human tumor antigens.[83-86] Metastatic human RCC cells have increased proportions of both $CD25^+$ Treg cells and $CCR4^+$ T cells relative to primary neoplastic cells in the kidney,[87] suggesting that selective depletion of CCR4 may lead to regression of metastatic lesions in mRCC. Denileukin diftitox[88] and the anti-CD25 monoclonal antibody daclizumab[89] have been shown to augment the effect of tumor an-

TABLE 1. Ongoing Trials of Combinations of PD-1/PD-L1 Inhibition and Angiogenesis or Other Immune Checkpoint Inhibitors in mRCC

PD-1/PD-L1 Inhibitor	Second Agent (Mechanism)	Phase	Estimated Enrollment	ClinicalTrials.gov Identifier
Nivolumab	BMS-986016 (anti-LAG-3)	I	168	NCT01968109
Pembrolizumab	Pazopanib (angiogenesis inhibitor)	I	228	NCT02014636
Pembrolizumab	Axitinib (angiogenesis inhibitior)	I	60	NCT02133742
Pembrolizumab	Ipilimumab (anti-CTLA4)	I/II	343*	NCT02089685
MEDI4736	Tremelimumab (anti-CTLA4)	I	102**	NCT01975831
MEDI4736	MEDI0680 (anti-PD-L1)	I	150**	NCT02118337
MPDL3280A	Bevacizumab (angiogenesis inhibitor), sunitinib (angiogenesis inhibitor)	II	300	NCT01984242
Nivolumab	Ipilimumab (anti-CTLA4)	III	1,070	NCT02231749

Abbreviations: PD-1, programmed death; PD-L1, programmed death ligand-1; mRCC, metastatic renal cell carcinoma; CTLA4, cytotoxic T lymphocyte associated protein-4.
*This study will enroll patients with both mRCC and metastatic melanoma.
**This study will enroll patients with various advanced solid malignancies (not solely mRCC).

tigen vaccination in a variety of solid malignancies, including breast cancer and mRCC. Further efforts to eliminate or inhibit Tregs may enhance the efficacy of immunotherapeutic strategies for mRCC.

mRCC Tumor Vaccines

Interest in vaccine therapies for the treatment of various malignancies has increased following FDA approval of the dendritic cell vaccine sipuleucel-T for metastatic castration-resistant prostate cancer.[90] In the specific context of mRCC, tumor vaccines may be of particular use in the noninflamed phenotype, as vaccination might be able to initiate a tumor-targeted immune response that would increase the initial trafficking of T cells to tumors.[26]

Several vaccines have been developed for clinical investigation of mRCC, including some targeted against peptide antigens (IMA901, TG-4010, and MVA-5T4)[91-96] and some developed from autologous dendritic cells (AGS-003). Of these, IMA901 and AGS-003 are currently in late-stage clinical trials.

Phase I and II studies of the multipeptide mRCC vaccine IMA901 have demonstrated encouraging overall survival in the subset of patients who also received a single dose of cyclophosphamide in addition to the vaccine.[97-98] A randomized phase III study of IMA901, cyclophosphamide, and GM-CSF plus sunitinib versus sunitinib alone as first-line therapy for patients with metastatic RCC is currently ongoing.[99]

AGS-003 is a personalized, autologous dendritic cell vaccine that has been examined in phase II clinical trials in combination with sunitinib. Preliminary data indicate improved progression-free survival and overall survival when compared to historic controls of patients with unfavorable-risk mRCC.[100-102] A randomized phase III trial of AGS-003 plus standard therapy (sunitinib) for metastatic RCC is currently recruiting participants.[103]

Recently, multiregion whole-exome sequencing, chromosome aberration analysis, and ploidy profiling of primary and metastatic RCCs have demonstrated substantial levels of intratumoral genetic heterogeneity in this disease.[104] Future re-

search into mRCC vaccines will attempt to exploit this intratumoral heterogeneity by targeting the tumor neoantigens that arise from such genetic diversity. A study of such a personalized neoantigen cancer vaccine ("Neovax") is currently recruiting participants and should enter phase I clinical trials for RCC in 2015.[105-106]

Ongoing studies will also address the optimal combinations and sequence of mRCC vaccines, targeted immunotherapy, and small-molecular inhibitors in an effort to further improve immune responses.

IMPROVING PATIENT SELECTION: DEVELOPING BETTER PREDICTIVE MODELS

The determination of appropriate biomarkers to better predict which patients with mRCC will benefit most from immunotherapy is an active area of investigation. Multiple clinical trials have indicated that responses to immunotherapy with checkpoint inhibitors have been observed both in patients whose tumors express PD-L1 and in those without such expression.[107-108] There are several potential explanations for this discrepancy, including: (1) heterogeneous expression of PD-L1 across the primary tumor and metastatic sites in individual patients, (2) inconsistent definitions of the threshold PD-L1 immunohistochemical positivity (e.g., 1% vs. 5% staining), (3) immunosuppressive effects of PD-L1 expression by other cells in the tumor microenvironment (e.g., macrophages or myeloid-derived suppressor cells), and (4) the potential impact of PD-L2 expression on responsiveness to anti-PD-1/PD-L1 therapy.

Preclinical and clinical trials of agents targeting PD-1/PD-L1 have used cutoffs of PD-L1 immunohistochemical positivity ranging from 1 to 5% staining, resulting in differences in response rates depending on which definitions are employed.[54] Standardization of the appropriate cutoff for a positive test will be essential for future development of meaningful predictive models.

Furthermore, a recent small series has demonstrated discordant PD-L1 expression between primary RCC sites and

metastatic RCC sites in 15% (5 of 33) of patients, suggesting that differential PD-L1 expression profiles between primary and metastatic lesions may contribute to the heterogeneity of responsiveness to anti-PD-1/PD-L1 targeted therapies.[109] In the setting of such heterogeneous PD-L1 expression, it is likely that the most useful models for prediction of response to immunotherapy will integrate PD-L1 status with other clinical, pathologic, molecular, and cytogenetic variables. These may include PD-L2 status,[110] gene expression profiling,[111] and/or clinical characteristics such as the Memorial Sloan Kettering Cancer Center (MSKCC) risk score[96] or International Metastatic RCC Database Consortium (IDMC or Heng) criteria.[112] Development of comprehensive predictive models for immunotherapy in mRCC is currently an active area of investigation.

CONCLUSION

Novel immunotherapies have produced encouraging initial results in the treatment of metastatic RCC; however, these agents are unlikely to be effective as monotherapy in the majority of patients. At present, intensive clinical study is focused on devising combinations of therapies and developing more accurate predictive biomarker models in an effort to improve clinical outcomes.

Disclosures of Potential Conflicts of Interest

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GENITOURINARY CANCER

Integrating New Approaches in Complicated Bladder Cancer

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New and Promising Strategies in the Management of Bladder Cancer

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OVERVIEW

Bladder cancer is a complex and aggressive disease for which treatment strategies have had limited success. Improvements in detection, treatment, and outcomes in bladder cancer will require the integration of multiple new approaches, including genomic profiling, immunotherapeutics, and large randomized clinical trials. New and promising strategies are being tested in all disease states, including nonmuscle-invasive bladder cancer (NMIBC), muscle-invasive bladder cancer (MIBC), and metastatic urothelial carcinoma (UC). Efforts are underway to develop better noninvasive urine biomarkers for use in primary or secondary detection of NMIBC, exploiting our genomic knowledge of mutations in genes such as *RAS, FGFR3, PIK3CA*, and *TP53* and methylation pathways alone or in combination. Recent data from a large, randomized phase III trial of adjuvant cisplatin-based chemotherapy add to our knowledge of the value of perioperative chemotherapy in patients with MIBC. Finally, bladder cancer is one of a growing list of tumor types that respond to immune checkpoint inhibition, opening the potential for new therapeutic strategies for treatment of this complex and aggressive disease.

Cancer is a genetic disease.[1] A cancer cell inherits or acquires mutations that enable it to grow efficiently, replicate indefinitely, support angiogenesis, avoid apoptosis, and in some cases, metastasize.[2] Molecular profiles obtained by host and tumor DNA sequencing, single nucleotide polymorphism, RNA, and protein microarrays, and methylation screens are helping to pinpoint which mutations drive the cancerous phenotype and which are merely passengers on the malignant journey. Notwithstanding the role of individual genes, aggregate molecular profiles provide patient- and tumor-specific information that details the biologic complexity of a particular cancer and can be exploited for its clinical implications, therapeutic insights, and diagnostic benefit.

DETECTION AND MONITORING OF BLADDER CANCER IN THE GENOMIC ERA

Although the treatment for UC has improved over the last several decades, diagnostic techniques have progressed more slowly. Cystoscopy is still considered the best method for diagnosing UC, but it is invasive, uncomfortable, and can only detect approximately 90% of lesions.[3] In addition, when a tumor is discovered and must be biopsied and/or removed, a second procedure is required, transurethral resection of the bladder tumor (TURBT), which requires general anesthesia. Last, the cost of cystoscopy, especially when used to monitor recurrence, is the major reason why per-patient expenses for

UC are among the highest for all cancers.[4] The major problem associated with NMIBC is that after initial TURBT, 50% to 70% of patients develop multiple recurrences; 10% to 20% of these will progress to MIBC.[5] This risk of recurrence and progression calls for life-long surveillance. The current standard procedure is to perform cystoscopy and evaluate urine cytology every 3 to 4 months in the first 2 years, twice per year in years 3 to 4, and yearly thereafter.[5]

The burden of this follow-up on the patient, as well as the direct and indirect costs for the patient and society in terms of lost wages, have led to extensive efforts to develop noninvasive urine biomarkers for UC. However, to date, none have demonstrated sufficient specificity and sensitivity to monitor the general population or replace cystoscopy and cytology in monitoring for recurrence.[6] Urine cytology is particularly insensitive for detecting low-grade tumors. However, advances in genomics have clearly demonstrated that DNA alterations offer great promise for detecting primary or secondary bladder cancer.

NMIBC and MIBC are genetically different.[7-10] NMIBC is characterized by a high frequency of mutations in the *FGFR3* oncogene, leading to constitutive activation of the RAS/ MAPK pathway. In MIBC, mutations in the *TP53* gene prevail. In general, mutations in *FGFR3* and *TP53* are mutually exclusive, suggesting that NMIBC and MIBC develop along different oncogenetic pathways. However, these mutations often occur simultaneously in stage pT1 tumors that invade the connective tissue layer underlying the urothelium. Re-

cently, somatic mutations in the *PIK3CA* oncogene, which encodes the catalytic subunit p110α of class-IA PI3 kinase, were described in 13% to 27% of bladder tumors.[11] These mutations often coincided with *FGFR3* mutations. Mutations in the *RAS* oncogenes (*HRAS*, *KRAS*, and *NRAS*) have also been found in 13% of bladder tumors and in all stages and grades; they are mutually exclusive with *FGFR3* mutations. Given these findings, analyzing urine sediment for genetic mutations may be a promising strategy for noninvasive detection of bladder cancer.

FGFR3

FGFR3 mutations occur in around 50% of both lower and upper urinary tract tumors, clustering in three distinct hotspots in exons 7, 10, and 15.[12] The most common mutations in exon 7 and 10 favor ligand-independent dimerization, transactivation, and signaling.[13-17] Mutations in exon 15 are rare and induce a conformational change in the kinase domain, resulting in ligand-independent receptor activation and signaling, as well as *FGFR3* cellular localization, with aberrant endoplasmic reticulum signaling.[18] *FGFR3* mutations are thought to occur early during urothelial transformation, as they are reported in over 80% of preneoplastic lesions,[13,14] pointing to an overall "benign" effect of *FGFR3* mutation in the bladder.[17,19] *FGFR3*-mutant tumors are more chromosomally stable than their wild-type counterparts. A mutually exclusive relationship between *FGFR3* mutation and overrepresentation of 8q was observed in NMIBC.[20] A recent study found that around 80% of NMIBC and 54% of MIBC have dysregulated *FGFR3* with discordant mutation and protein expression patterns, suggesting a key role for *FGFR3* in both NMIBC and MIBC, either through mutation, overexpression, or both.[21] These discrepancies may reflect differential downstream signaling of wild-type and mutant receptors or the different molecular pathways instigating the development of these tumors. The mechanisms driving *FGFR3* overexpression in UC are largely unknown, although a recent study demonstrated the regulation of *FGFR3* expression in urothelial cells by two microRNAs (miR-99a/100) that are often downregulated in UC, particularly in low-grade and low-stage tumors.[22]

FGFR3 mutations were among the first to be used as urine biomarkers of recurrent disease, especially low-grade disease, which is challenging to detect by urine cytology. van Rhijn et al[23] reported that combined microsatellite and *FGFR3* mutation analysis could detect UC in voided urine. *FGFR3* mutations were found in 44% of urothelial tumors (59 tumors), but were absent in 15 G3 tumors. The sensitivity of microsatellites to detect cancer in voided urine was lower for tumors harboring *FGFR3* mutations (15 out of 21 tumors; 71%) than for *FGFR3* wild-type UC (29 out of 32 tumors; 91%). By including the *FGFR3* mutation, the sensitivity of molecular cytology increased from 71% to 89% and was superior to the sensitivity of morphologic cytology (25%) for every clinical subdivision. These findings highlighted the potential of molecular biology as an adjunct to cystoscopy and cytology in informing follow-up care.

HRAS

The *HRAS* gene, which codes for p21 Ras (or Ras), a small GTPase, was the first identified human oncogene. It was found in the T24/EJ urothelial cell line.[24-26] In the normal urothelium, normal Ras protein diminishes with differentiation, with highest expression in the basal (progenitor) cells.[27] The role of Ras in UC is supported by its ability to transform Simian vacuolating virus 40 (SV40)-immortalized human urothelial cells into invasive transitional-cell carcinomas.[28,29] In addition, in elegant transgenic studies, Ras overexpression has been shown to lead to NMIBC.[30] Ras interacts with Raf, a serine/threonine kinase, which is activated in tumor cells containing enhanced growth signaling pathways in both NMIBC, MIBC, and metastatic disease with subsequent activation of MAPK.[31,32]

P53

The p53 tumor suppressor encoded by the *TP53* gene located on chromosome 17p13.1[33] inhibits phase-specific cell cycle progression (G1-S) through transcriptional activation of p21$^{WAF1/CIP1}$.[34] Most UCs exhibit loss of a single 17p allele. Additional mutations in the remaining allele can inactivate *TP53*, leading to increased nuclear accumulation of the mutant protein, which has a longer half-life than its wild-type counterpart.[35] *TP53* deletion was correlated with grade and stage of UC.[36-41] Invasive carcinoma can also progress from recurrent papillary carcinoma by acquiring additional alterations in *TP53*, *RB1*, *PTEN*, *EGFRs*, *CCND1*, *MDM2*, or *E2F*.[42] In addition, oncogenic HRas has been shown to promote the malignant potency of UC cells that have acquired

deficiencies of *TP53*, *RB1*, and *PTEN*.[42] Mutations in the *TP53* gene that result in a truncated protein (or no protein), homozygous deletion of both alleles of the gene, or gene silencing by methylation of the promoters of both alleles cannot be detected by nuclear accumulation of p53 protein,[43,44] thus limiting the sensitivity of immunohistochemistry (IHC) for p53 alterations. Notwithstanding this caveat, overexpression of nuclear p53 protein by IHC has been used as a surrogate marker for detection of mutant p53 in clinical specimens. The expression of p53 has been associated with increased risk of progression of NMIBC or mortality in patients with MIBC, independent of tumor grade, stage, and lymph node status.[33,34,45-56] Interestingly, in a recently reported randomized, prospective trial, this was not borne out in patients treated with cystectomy.[57] In this and other studies, discordance in the identification of p53 as an independent prognostic marker for UC progression, recurrence, mortality, and response to therapy may be a result of patients' genetic and epigenetic status, cohort selection, and technical and statistical variations.[41,58-60]

COMBINING GENOMIC ASSAYS

To develop more sensitive and specific assays, recent studies have simultaneously evaluated *RAS, FGFR3,* and *PIK3CA* in UC.[61] A study of 257 patients with primary bladder tumors found that 64% (164 out of 257) of tumors contained an *FGFR3* mutation, 11% (28) samples were mutant for one of the *RAS* genes, and 24% (61) harbored a *PIK3CA* mutation.[61] Of the 257 primary tumors, 26% overexpressed p53, which is indicative of missense mutations, as noted above. When *RAS, FGFR3,* and *PIK3CA* mutations were calculated with *TP53* mutations, only 27 tumors (11%) were wild-type for all examined genes. In 54 patients who developed one or more recurrences, tissue was available from 184 recurrent tumors, including multifocal recurrences. Using the SNaPshot-based mutation assay, investigators examined these tumors for *FGFR3, PIK3CA,* and *RAS* mutations. The frequency of p53 overexpression was low (6 out of 54) in the primary tumors of this group of patients, consisting mainly of NMIBC tumors. In patients with a wild-type primary tumor, recurrences were mostly wild-type (49 out of 54), whereas five harbored an *FGFR3* mutation. One recurrent tumor contained two different *PIK3CA* mutations. In recurrences, *PIK3CA* mutations in addition to an *FGFR3* mutation were associated with higher-grade tumors compared with recurrences harboring an *FGFR3* mutation alone. Importantly, there was 100% consistency in the type of mutation for *RAS* and *PIK3CA* among different tumors in the same patient.

Investigators also developed a methylation assay for specific detection of recurrent NMIBC in voided urine.[62] Microsatellite analysis was also used to detect loss of heterozygosity in voided urine samples.[23] Mutation analysis of *FGFR3, PIK3CA, HRAS, KRAS,* and *NRAS* was recently combined with methylation-specific assays to determine whether this combination outperformed either examination alone.[63] Results were compared with those of urine cytology in a large, retrospective, longitudinal co-

hort that was part of the European FP7 UROMOL project. A total of 716 voided urine samples from 136 patients with NMIBC (Ta/T1, G1/2) were collected at TURBT. Patients with a history of carcinoma in situ were excluded from the analysis. Urine was collected at regular follow-up visits immediately before cystoscopy. During follow-up, 552 histologically proven recurrences were detected, including mainly stage Ta (92%), G1/2 (82%), and solitary tumors (67%). Sensitivity for detecting a recurrent tumor varied between 66% and 68% for the molecular tests after patient stratification based on tumor DNA analysis. A combination of markers increased sensitivity, but decreased the number of patients eligible for a certain test combination. Combining urine cytology with *FGFR3* analysis without stratifying for *FGFR3* status of the incident tumor increased sensitivity from 56% to 76%.

This study highlights the challenge of molecular examination of urine using genomics, and the importance of including all available information (i.e., cytology). However, there is no doubt that next-generation exome sequencing of paired tumor and peripheral blood samples will uncover many more potential biomarkers that could be added to these panels to improve their performance. Such examination was first performed in 2011 in a small set of patients.[9] Initial findings from this cohort were examined in light of findings from an additional 88 patients with bladder cancer[10] and by the The Cancer Genome Atlas (TCGA) consortium.[64] From these contributions, several previously defined mutations were observed (in *TP53, RB1,* and *HRAS*), but novel mutations were also noted, the most common of which was in *UTX,* which was identified in 21% of tested individuals. Of note, most of the identified new mutations were related to chromatin remodeling, suggesting a potential new area for bladder cancer research. Mutations in chromatin remodeling genes are commonly found in several other cancer types, suggesting their fundamental contribution to carcinogenesis. Adding to this complexity is a recent study of 537 patients with locally advanced or metastatic UC of the bladder, 74 patients with nonbladder, and 55 patients with nonurothelial bladder cancers profiled using mutation analysis, in situ hybridization, and IHC assays.[65] Compared with nonbladder UC, bladder UC exhibited more frequent expression of abnormal protein (and increased amplification) in HER2, androgen receptor, serum protein acidic and rich in cysteine (SPARC), and topoisomerase 1. These findings suggest that bladder UC has higher levels of actionable biomarkers that may have clinical implications for treatment and diagnostic options.

NEOADJUVANT AND ADJUVANT CHEMOTHERAPY IN MUSCLE-INVASIVE BLADDER CANCER

Approximately 25% of patients with bladder cancer present with a tumor invading the muscle layer of the bladder wall (T2 to T4).[66] MIBC is associated with a high rate of recurrence and poor overall prognosis, despite aggressive local and systemic therapies. Radical cystectomy is the standard treatment for MIBC, but even with substantial improvements in surgical techniques, mortality remains high because of a high

TABLE 1. Summary of Phase III Perioperative Cisplatin-Based Chemotherapy Clinic Trials in Patients with Muscle-Invasive Bladder Cancer

	Stadler (p53)	Cognetti	Paz-Ares	Sternberg	Grossman	MRC/EORTC
Chemotherapy	Adjuvant MVAC × 3	Adjuvant GC × 4	Adjuvant PGC × 4	Adjuvant ddMVAC/ GC/MVAC × 4	Neoadjuvant MVAC	Neoadjuvant CMV
Patients	T1 and T2 negative LN	T2G3, T3 to T4, N0-2	T3 to T4, N0 to N2	T3 to T4 and/or pT × N1 to N3	T2 to T4aN0	T2 to T4aN0
Design						
α error	5%	5%	5%	5%	5%	5%
Power	90%	80%	80%	80%	80%	90%
Endpoint	Recurrence	OS	OS	OS	OS	OS
	0.5 to 0.3 at 3 years (20%)	50% to > 60% at 2 years (10%)	50% to > 65% at 2 years (15%)	35% to > 42% at 5 years (7%)	35% to > 42% median OS (50%)	50% to > 60% at 2 years (10%)
Hazard Ratio	0.52	0.75	0.77	0.826		
Planned Sample Size	190	610	340	660 (originally 1,344)	298	915
Results						
Patients randomized	114 (499 tested and 272 +p53)	192	142	284	307	976
Years to Accrue	9	6	7	6	11	6
5-Year Recurrence (Observation vs Chemotherapy)	TTR, 0.20; p = 0.62; HR, 0.78	DFS, 42.3% vs. 37.2%; p = 0.70; HR, 1.08; all, 40%	3 years 44% vs. 73%; p < 0.0001; HR, 0.36; all, 54%	PFS, 31.8% vs. 47.6%; p = < 0.0001; HR, 0.54		5-year DFS, 32% vs. 39%; 10-year DFS, 20% vs. 27% p = 0.008; HR, 0.82
5-Year OS (Observation vs. Chemotherapy)	85% (both arms)	53.7% vs. 43.4%; p = 0.24; HR, 1.29; all, 48.5%	31% vs. 60%; p < 0.0009; HR, 0.44; all, 49%	47.7% vs. 53.6%; p = 0.13; HR, 0.78; all, 38.6%	43% vs. 57%; p = 0.06	5-year OS, 43% vs. 49%; 10-year OS, 30% vs. 36%; p = 0.037; HR, 0.84
Median Follow-up	5.4 years	35 months	30 months	7 years	8.7 years	8 years

Abbreviations: CMV, cisplatin/methotrexate/vinblastine; dd, dose-dense; DFS, disease-free survival; EORTC, European Organisation for Research and Treatment of Cancer; GC, gemcitabine/cisplatin; HR, hazard ratio; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; OS, overall survival; PFS, progression-free survival; PGC, paclitaxel/gemcitabine/cisplatin; TTR, time to progression.

rate of systemic failure. The 5-year mortality rate for patients with MIBC is about 50% to 70%.[67,68] MIBC behaves as a systemic disease, and therefore needs systemic therapy early in the disease process to eradicate micrometastases.[69]

Phase III clinical trials of neoadjuvant cisplatin-based chemotherapy have demonstrated a survival benefit in patients with MIBC,[67,70,71] mainly by pathologic down-staging of muscle-invasive tumors (stage T2 to T4a) to nonmuscle-invasive tumors (< T2).[67,72-74] In the randomized Southwest Oncology group 8710 trial, neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) followed by cystectomy demonstrated a 77-month median survival compared with a 46-month median survival with cystectomy alone. In this study, the likelihood of long-term survival was over 85% at 5 years for patients who achieved pathologic down-staging to pT0 either by TURBT alone before cystectomy or by the addition of neoadjuvant MVAC chemotherapy. However, long-term survival was less than 40% at 5 years in patients with residual muscle-invasive tumors (> pT2) at the time of cystectomy in both treatment arms.[67] Patients who do not respond to neoadjuvant chemotherapy have a poor prognosis. However, no data demonstrate a survival benefit for additional chemotherapy in the adjuvant setting after three to four cycles of neoadjuvant cisplatin-based chemotherapy. Large clinical trials are currently in development in this setting.

Data for adjuvant chemotherapy[57,75-77] are less compelling than for neoadjuvant chemotherapy. However, some patients benefit from adjuvant chemotherapy, including those who received up-front radical cystectomy and have extensive tumor invasion of the bladder wall or lymph node involvement. European Organisation for Research and Treatment of Cancer (EORTC) 30994 was a phase III trial of adjuvant versus delayed chemotherapy after cystectomy for patients with pT3 to T4 or node-positive disease.[77] The study randomly assigned 298 patients to one of three adjuvant cisplatin-based chemotherapy regimens (MVAC, high-dose MVAC, or gemcitabine/cisplatin) or observation and chemotherapy at relapse. After a median follow-up of 7 years, 66 out of 141 patients (47%) in the adjuvant chemotherapy arm had died compared with 82 out of 143 (57%) in the observation arm. No significant improvement in overall survival was noted with adjuvant chemotherapy compared with observation (adjusted hazard ratio [HR] 0.78; 95% CI, 0.56 to 1.08; p = 0.13). However, adjuvant chemotherapy significantly prolonged progression-free survival compared with observation (HR 0.54; 95% CI, 0.4 to 0.73, p < 0.0001), with a 5-year progression-free survival rate of 47.6% (95% CI, 38.8 to 55.9) in the adjuvant chemotherapy arm and 31.8% (95% CI, 24.2 to 39.6) in the observation arm. Although this study did not meet its accrual goal of 644 patients and was terminated early, it is the largest randomized adjuvant trial to date. Although the study

was limited in power to show a significant improvement in overall survival with adjuvant chemotherapy, it is possible that some subgroups of patients might benefit from adjuvant chemotherapy. Cisplatin-based neoadjuvant chemotherapy remains the standard of care in MIBC. Table 1 summarizes neoadjuvant and adjuvant clinic trials in MIBC.

IMMUNE CHECKPOINT INHIBITION IN SOLID TUMORS

Immune checkpoint inhibition for cancer treatment is an area of growing research. Immune checkpoint pathways regulate T-cell activation to escape antitumor immunity. Immune checkpoint molecules involved in this mechanism include CTLA-4, programmed cell death 1 (PD-1) and its ligands PD-L1 and PD-L2, T-cell immunoglobulin mucin-3, and lymphocyte activation gene-3.[78] Ipilimumab, a monoclonal antibody targeting CTLA-4, a potent immune checkpoint molecule expressed on T cells, demonstrated a survival benefit in a phase III study of patients with metastatic melanoma.[79] PD-1 is an immune inhibitory receptor expressed on several immune-cell subsets, particularly cytotoxic T cells.[80] PD-1 interacts with PD-L1 (B7-H1, CD274), which is expressed on tumor cells and immune cells, including T cells.[81,82] Recent studies have demonstrated that upregulation of PD-L1 is an important mechanism of immune escape in NMIBC.[83-86] Overexpression of PD-L1 in UC correlates with high-grade disease and worse clinical outcome. Anti-PD-1 and anti-PD-L1 have an improved toxicity profile compared with historic data from anti-CTLA-4 clinical trials.[87,88] In September 2014, the U.S. Food and Drug Administration (FDA) granted accelerated approval of pembrolizumab for the treatment of unresectable or metastatic melanoma, and in December 2014 granted accelerated approval to nivolumab for unresectable or metastatic melanoma refractory to standard therapy.

TREATMENT OF METASTATIC BLADDER CANCER

The treatment options for metastatic UC are very limited; however, progress has been made in treating metastatic transitional carcinoma of the urothelial tract with combination chemotherapy. The median survival of 15 to 18 months with either MVAC or gemcitabine/cisplatin is substantially better than the 6 to 9 months with single-agent chemotherapy. In fact, 5% of patients have a complete, sometimes durable, remission.

CLINICAL STUDIES OF PD-1/PD-L1 INHIBITORS IN UROTHELIAL CARCINOMA

Two clinical trials of checkpoint inhibitors have reported preliminary efficacy in advanced/refractory metastatic UC. Remarkable efficacy and safety was seen in a phase I expansion cohort of 67 patients with heavily pretreated metastatic bladder cancer. Patients received 15 mg/kg of MPDL3280A, a human monoclonal antibody to PD-L1 containing an engineered Fc-domain, later revised to a flat dose of 1,200 mg intravenously every 3 weeks.[89] Response rates were reported by PD-L1 positivity status, defined as 5% or higher of tumor-infiltrating immune cells staining for PD-L1 by IHC.[1] In this study, 27% of tumors were IHC 2- or 3-positive, as defined by expression of PD-L1 on tumor-infiltrating immune cells. The overall response rate for all patients by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was 26%, and was even more remarkable (43%) among patients with PD-L1$^+$ tumor-infiltrating cells. Even among patients whose tumor infiltrating immune cells were PD-L1$^-$, the response rate was 11% as measured by RECIST v1.1. The median time to first response was 42 days (range, 38 to 85 days). Based on these results, MPDL3280A received breakthrough designation by the FDA in June 2014.

A phase I trial of pembrolizumab/MK-3475, a PD-1 inhibitor, studied 33 patients with advanced UC expressing PD-L1 in at least 1% of tumor cells by IHC. Patients received 10 mg/kg of pembrolizumab every 2 weeks. A response was seen in 7 out of 29 (24%) evaluable patients, and 64% of patients experienced a decrease in target lesions.[90] With a median follow-up of 11 months, six patients have ongoing responses (median duration 16 to 40 weeks; median not reached).

Multiple PD-1/PDL-1 agents are currently being tested alone or in combination in advanced/refractory UC. Many more trials are in development in earlier disease states, testing agents such as MPDL3280A (NCT02302807) in the first-line setting in cisplatin-ineligible patients with metastatic bladder cancer, nivolumab in the maintenance setting after first-line cisplatin-based chemotherapy, and pembrolizumab in patients with NMIBC (NCT02324582).

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GYNECOLOGIC CANCER

Cervical Cancer from Diagnosis to Survivorship

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Nonsurgical Management of Cervical Cancer: Locally Advanced, Recurrent, and Metastatic Disease, Survivorship, and Beyond

Helen J. Mackay, MD, Lari Wenzel, PhD, and Linda Mileshkin, MD

OVERVIEW

Despite the declining incidence of cervical cancer as a result of the introduction of screening programs, globally it remains a leading cause of cancer-related death in women. Outcomes for patients who are diagnosed with anything but early-stage disease remain poor. Here we examine emerging strategies to improve the treatment of locally advanced disease. We discuss emerging biologic data, which are informing our investigation of new therapeutic interventions in persistent, recurrent, and metastatic cervical cancer. We recognize the importance of interventions to improve quality of life and to prevent long-term sequelae in women undergoing treatment. Finally, and perhaps most importantly, we recognize the need for global collaboration and advocacy to improve the outcome for all women at risk of and diagnosed with this disease.

Cervical cancer remains one of the leading causes of cancer-related morbidity and mortality worldwide and is the fourth leading cause of cancer death in women.[1] Human papillomavirus (HPV), particularly types 16 and 18, is associated with subsequent development of cervical cancer, with an increased risk also seen among smokers.[2] The incidence and mortality rates of cervical cancer are substantially higher in resource-poor regions of the world; the age standardized incidence of cervical cancer being 1.6 times higher in less developed countries. These regional discrepancies are attributable to reductions made in the incidence of cervical cancer in resource-rich countries with the introduction of widely accessed screening programs.[3] This decline is expected to continue as a result of the implementation and increased availability of vaccination against HPV.[4] These gains, however, remain challenging to replicate in resource-poor regions, which lack the infrastructure and funding to implement screening and vaccination programs, and where access to treatment remains an important problem. Within the United States, over 12,000 women will be diagnosed with cervical cancer in 2015 with approximately 4,000 women expected to die from their disease. Cervical cancer is disproportionately more common in women of African American or Hispanic ethnicity and in patients with limited access to health care.[3] Despite the advances in cervical cancer prevention and diagnosis, the outcome for patients diagnosed with later-stage and recurrent disease remains poor.

NONSURGICAL MANAGEMENT OF LOCALLY ADVANCED CERVICAL CANCER

The use of low-dose chemotherapy concurrent with pelvic radiation has been proven to improve survival, and became the established standard of care for locally advanced cervical cancer after the National Cancer Institute issued a clinical alert in 1999 about the benefit of chemoradiation compared with radiation alone as observed in five randomized clinical trials.[5] The Medical Research Council (MRC) individual patient data meta-analysis found that the addition of concurrent chemotherapy to radiation increased the 5-year overall survival (OS) rate by 6% (hazard ratio [HR], 0.81; 60% vs. 66%).[6] On the basis of the studies in this analysis, weekly cisplatin at a dose of 40 mg/m^2 during pelvic radiation has been adopted as the standard of care for the treatment of locally-advanced disease. However, the 5-year disease-free survival rate was only 58% in the chemoradiation group, which although superior to 50% with radiation alone, still leaves substantial room for improvement.

Identifying Patients Most at Risk of Recurrent Disease

The main prognostic factor for outcome in cervical cancer has traditionally been the International Federation of Gynecology and Obstetrics (FIGO) staging system, which is based on clinical examination alone. In those with FIGO stage 1B2 or higher, treatment with primary chemoradiation in the recommended approach.[7] In the meta-analysis, the additional benefit of chemotherapy was seen regardless of age, tumor histology, or grade. However, there appeared to be a lesser degree of benefit in higher staged tumors, with an absolute 5-year survival benefit of 10% for women with stages Ib to IIa cervical cancer, 7% for those with stage IIb, and 3% for women with stage III to IVa disease.[6]

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In the meta-analysis, a benefit of adding chemotherapy was also seen regardless of nodal involvement, although it was only possible to look at this in five of the 18 included trials. However, Narayan et al and others have highlighted the important prognostic role of both nodal and uterine corpus involvement as detected by imaging, with MRI and PET now accepted modalities for noninvasively determining these features.[8-10] Nodal involvement has been documented to predict disease relapse in multiple studies, but is not part of the current FIGO staging system.[8,11-14] Uterine corpus invasion tends to be associated with tumors that grow endophytically rather than exophytically, and has also been shown to predict worse outcomes, in part because it predicts nodal metastasis (Fig. 1).[15-20] The relapse rate in those with PET-positive node disease has been reported to be approximately 50% after standard chemoradiation.[17,21,22] Some suggest that a follow-up fludeoxyglucose (FDG)-PET scan done 3 to 4 months postchemoradiation can predict patient outcome and may help to determine the intensity of follow-up needed.[23]

Optimizing Local Therapy

Although the development of distant disease after chemoradiation is the predominant cause of mortality, local relapse may also be a problem that causes substantial morbidity. Although the patterns of treatment failure have not been well described in all studies, in the meta-analysis, locoregional treatment failure was responsible for 35% of the failure events across trials.[6]

Standard radiation treatment involves 40 to 50.4 Gy of external beam radiation therapy (EBRT) delivered in fractions of 1.8 to 2 Gy to the pelvis. The upper border for treatment is usually L4-S1, unless an extended field is required to cover involved node disease. Parametrial or nodal boost may also

KEY POINTS

· Cervical cancer remains one of the leading causes of cancer-related morbidity and mortality in women worldwide.

· A number of ongoing clinical trials are examining the role of adjuvant chemotherapy in addition to the standard-of-care treatment, low-dose chemotherapy (cisplatin) concurrent with pelvic radiotherapy for locally advanced cervical cancer.

· Women undergoing treatment for locally advanced cervical cancer experience significant psychosocial distress. Multidisciplinary supportive care may reduce the magnitude of long-term sequelae and improve quality of life.

· Outcome for women diagnosed with metastatic or recurrent cervical cancer remains poor; there are a number of potential therapeutic targets actively under investigation. The first biologic agent, in combination with chemotherapy, to show a survival benefit was bevacizumab.

· International collaboration and engagement of medically underserved communities are essential to making progress in the treatment of cervical cancer.

FIGURE 1. Infiltrative versus Expansile Cervical Cancer
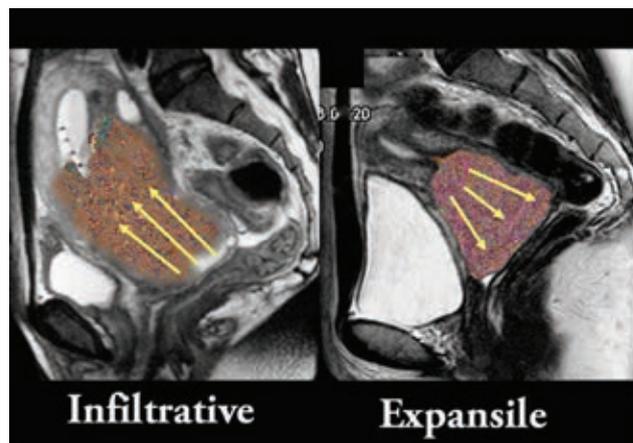
Infiltrative corpus invasive cervix cancer has higher local failure rates, increased frequency of nodal metastases at presentation, and poor survival compared with exophytic tumor of similar volume.

be given if these areas are involved. In addition to EBRT, brachytherapy direct to the primary tumor is considered to be an essential component of therapy. It is recommended that the overall treatment time for chemoradiation should not exceed 8 weeks. The role for intensity modulated radiation therapy (IMRT) is controversial and an area of active research because of the recognition that the cervix moves as a result of changes in bladder and bowel filling, and uterine movement.

There is also ongoing controversy about the best approach to delivery of brachytherapy. Traditionally, brachytherapy has been planned to give a recommended cumulative dose of 80 to 90 Gy EBRT and brachytherapy to "point A," which is an anatomic landmark 2 cm lateral to the central canal of the uterus and 2 cm up from the mucous membrane of the lateral fornix in the axis of the uterus.[24] There has also been increased interest in the value of using conformal brachytherapy, in which the dose is prescribed to the residual tumor volume at the end of EBRT rather than to point A. Proponents report that this approach may increase the effectiveness of local treatment and also reduce toxicity.[25] It is also recommended that image-guidance using either MRI or ultrasound is used to ensure that the tandem and ovoids used for the delivery of brachytherapy are correctly positioned within the uterus (Fig. 2).

A variety of approaches to intensifying the concurrent chemotherapy component of chemoradiation have been tested including the addition of cytotoxic agents. To date, no chemotherapy regimen has been found to be superior to 40 mg/m^2 (for most of the GOG studies, the does was capped at a maximum of 70 mg) of cisplatin weekly. However, the meta-analysis does suggest that substituting other agents that have demonstrated efficacy such as carboplatin or 5-flurouracil (5-FU) should be considered for women with a contraindication to cisplatin.[6] Addition of biologic agents to chemoradiotherapy is an active area of research. Despite suc-

FIGURE 2. Ultrasound and MRI Images for Delivery of Brachytherapy

The left ultrasound image shows the tandem position and superimposed isodoses in the treatment position. The ultrasound images correlates very well with the corresponding MRI image.

cess in head and neck cancers, the combination of the epidermal growth factor receptor (EGFR) inhibitor cetuximab, cisplatin, and radiotherapy proved toxic in patients with cervical cancer.[26] RTOG 0417 investigated 10 mg/kg of intravenous bevacizumab every 2 weeks (for three doses only) in combination with chemoradiation in 47 patients.[27] Results were promising and the toxicity profile was acceptable with no perforations or fistulas observed; further investigation is warranted.[28]

Multidisciplinary care is essential during chemoradiation for cervical cancer. In addition to monitoring side effects such as diarrhea and nausea, given the nature of the disease and the patient demographic, financial and psychosocial concerns are common. Early involvement of social work and psychology may assist women to cope with these issues. Younger women may require referral to discuss options for fertility preservation and hormone-replacement therapy. Smoking cessation is highly encouraged as ongoing smoking during chemoradiation may reduce the effectiveness of treatment, as well as increase the risk for the development of a second malignancy.[29] Treatment of anemia may also be required and it is generally recommended that the hemoglobin is maintained at 10 g/dL or higher during treatment.[30] Erythropoietin during chemoradiation, however, is not recommended because of an increased risk of thromboembolic events.[31]

Adjuvant Chemotherapy

Although chemoradiation is effective treatment for the primary disease, relapsed disease most commonly develops as distant metastatic disease.[32] It is therefore reasonable to predict that the addition of further cycles of adjuvant chemotherapy following completion of chemoradiation may decrease the development of distant metastases and thus improve survival. GOG109 was a U.S. study that randomly assigned patients who had been initially treated with radical hysterectomy and pelvic lymphadenectomy, and subsequently found to have positive pelvic nodes and/or positive margins and/or microscopic parametrial involvement, to receive adjuvant radiation alone or adjuvant chemoradiation. The chemotherapy consisted of four cycles of cisplatin and 5-FU, given as two cycles concurrent with radiation and two

cycles post radiation. Progression-free survival (PFS) and OS rates were substantially improved for patients who received the additional chemotherapy. Although only 60% completed all planned chemotherapy, a higher number of chemotherapy courses was positively associated with improved survival rates.[33] This trial was one of two trials considered in a subset analysis of the MRC meta-analysis that considered the potential value of giving additional adjuvant chemotherapy. In this subset, there was an impressive absolute improvement of 19% in 5-year survival (from 60% to 79%) compared with radiation alone.[33,34]

More recently, Duenes-Gonzalez et al demonstrated a benefit of adding concurrent gemcitabine to the standard regimen of weekly cisplatin during radiation, followed by two further cycles of adjuvant cisplatin/gemcitabine. This multicenter, randomized, phase III trial showed a significant 9% improvement in the primary outcome of PFS at 3 years (65% to 74%; p = 0.029).[35] Toxicity, however, was a concern with two deaths in the experimental arm and a doubling of grade 3 to 4 adverse events (86.5% vs. 46.3%). In addition, prior investigators had been unable to safely deliver similar doses of drugs combined with radiotherapy in a North American population. Furthermore, it remains unclear how much of the benefit observed in this trial was a result of the additional chemotherapy given following the chemoradiation. Finally, follow-up data were truncated at 1 year, and as a result, an accurate measure of the effect on OS or rate of serious late complications cannot be properly assessed.[36]

Although not practice changing, these studies do raise important and unresolved questions regarding the potential value of adjuvant chemotherapy for women with locally advanced cervical cancer.

Current Clinical Trials

The Gynecologic Cancer InterGroup (GCIG) has an ongoing series of international, randomized, phase III trials aiming to test the effect of different chemotherapy strategies during chemoradiation on OS rates. The OUTBACK trial, led by the Australia New Zealand Gynaecological Oncology Group (ANZGOG) in collaboration with NRG Oncology, is testing the value of administering additional adjuvant chemotherapy after standard cisplatin-based chemoradiation compared with chemoradiation alone (ACTRN12610000732088). The primary aim is to determine if the addition of four cycles of adjuvant carboplatin and paclitaxel to standard cisplatin-based chemoradiation can improve OS.

The TACO trial, led by the Korean Gynecologic Oncology Group (KGOG) and Thai Cooperative Group, is comparing standard treatment with weekly cisplatin during chemoradiation to 3-weekly cisplatin (NCT01561586). This is based on a prior phase II trial from the KGOG, which suggested that the triweekly cisplatin maybe more effective and feasible to deliver.[37] It may also be an attractive regimen to use in low-resource countries because of the reduced number of chemotherapy treatments required.

Finally, INTERLACE, a trial led by the National Cancer Research Institute in the United Kingdom, is testing the value of

administering additional neoadjuvant chemotherapy before chemoradiation compared with chemoradiation alone (NCT01566240). Although a previous meta-analysis suggested no improvement in OS with neoadjuvant chemotherapy in locally advanced cervical cancer, there was a suggestion of improved outcomes in those trials with a shorter cycle length of 14 days or less or higher dose intensity of cisplatin.[38] The regimen being tested of six doses of weekly carboplatin and paclitaxel before standard chemoradiation has been shown to be feasible to deliver in a prior phase II study.[39]

QUALITY OF LIFE FOR PATIENTS WITH CERVICAL CANCER AFTER TREATMENT

Cervical cancer survivors often experience substantial quality of life (QOL) disruptions associated with the disease and treatment, many of which persist long into survivorship.[40-45] A recent analysis of health-related QOL data among U.S. cancer survivors indicates that cancer survivors are more likely to have poor physical and mental health–related QOL (25% and 10%, respectively > 1 standard deviation above the U.S. population mean) compared with adults with no cancer history (10% and 5%, respectively). Furthermore, cervical cancer survivors and short-survival cancer survivors report the worst mental health–related QOL.[46]

Persistent sequelae include pain, bladder and bowel dysfunction,[47-51] sexual dysfunction,[52-56] lymphedema, and menopausal symptoms,[57] as well as reproductive concerns among women of childbearing age.[45,58-62] Adverse psychologic consequences are shared with women diagnosed with other gynecologic tumors, and include depression and anxiety,[63] sleep disturbance, and concentration difficulties to a greater magnitude than many other populations of patients with cancer.[41,42,64-68] Despite challenges inherent in this cancer survivor population, supportive interventions may assist in substantially improving QOL, with potential to also improve stress-related biomarkers.[69] This could, in turn, improve disease outcomes.[70-72]

A recent study indicated that of patients with cervical cancer diagnosed 9 to 30 months earlier, patients who reported the worst QOL also reported more gynecologic problems and less social support.[73] Gynecologic problems were substantially worse in patients treated with radiation with or without chemotherapy compared with those treated with surgery only, with a moderate-to-large effect size which is both statistically significant and clinically relevant (FACT-Cx, p = 0.014; FACT-TOI, p = 0.006). Treatment with radiation with or without chemotherapy also contributed to substantially poorer QOL, higher perceived stress, and greater depression, with modest-to-moderate effect sizes. Further, patients with three or more comorbidities before cancer diagnosis have also been reported to have substantially worse QOL, higher perceived stress, more depression and anxiety, and lower social support. In identifying subpopulations who are likely to benefit from supportive care interventions, it appears that a brief screening of type and number of premorbid medical problems, including mood disorders, could target the patients who have the greatest need for more immediate care and attention, as well as future cancer control studies. Therefore, further study of supportive care interventions to improve distress and decrease gynecologic problems in this vulnerable population appear warranted, particularly for women whose cancer treatment extends beyond surgery.

A recent supportive care study examined the effect of a psychosocial telephone counseling (PTC) intervention on QOL domains and associations with biomarkers. In this randomized clinical trial, after adjusting for age and baseline scores, participants receiving PTC had significantly improved depression and improved gynecologic and cancer-specific concerns at 4 months compared with usual care participants (all p < 0.05); significant differences in gynecologic and cancer-specific concerns (p < 0.05) were sustained at 9 months. Participants with decreasing interleukins-4, -5, -10, and -13 had substantially greater improvement in QOL than patients with increasing cytokine levels. This trial confirms that PTC benefits mood, QOL regarding cancer-specific and gynecologic concerns, for a multiethnic underserved cancer survivor population. The improvement in patient-reported outcomes with decreases in T-helper type 2, and counter-regulatory cytokines support a potential bio-behavioral pathway relevant to cancer survivorship.[74] Providing supportive care during treatment, and evaluating the effects of supportive care, may reduce the prevalence and magnitude of long-term sequelae of cervical cancer, which will in turn improve QOL and quality of care.

TREATMENT OF METASTATIC OR RECURRENT CERVICAL CANCER

Patients with distant metastases and/or with recurrent disease not suitable for local control have a very poor prognosis, with 5-year survival rates between 5% and 15%.[75] In this setting, any treatment is palliative, aiming to prolong survival but also to maintain or improve QOL. Platinum-based combinations have shown the most promising response rates with the combination of cisplatin (or carboplatin) with paclitaxel considered the standard of care. Responses to platinum-based chemotherapy are short-lived; median OS is around 12 months[76] and can be less than 6 months for those women who have poor prognostic features.[77] Response to chemotherapy is influenced by site of recurrence in relation to previous treatment, with progressive disease within a previously irradiated field being particularly resistant to cytotoxic agents.[78] Receipt of prior platinum-based chemoradiation and a short time to relapse after primary treatment are also important negative prognostic factors. There are no effective second-line chemotherapy options for women whose disease progresses.

Targeting Angiogenesis

Persistent HPV infection leads to neovascularization and tumor growth promotion, with many studies having demon-

strated a prognostic role for vascular endothelial growth factor (VEGF) and other markers of increased angiogenesis in cervical cancer (Fig. 3).[79-89] Targeting angiogenesis has therefore emerged as a rational therapeutic strategy in the treatment of cervical cancer. Early phase clinical studies with the anti-VEGF antibody bevacizumab, either alone or in combination with chemotherapy, suggested promising activity. Toxicity was acceptable and responses seen even in previously irradiated sites of disease.[89-91] As a result, a four-arm prospective, randomized clinical trial, GOG 240, was conducted. Over 400 patients were randomly assigned to receive treatment with one of two chemotherapy regimens: cisplatin plus paclitaxel versus paclitaxel plus topotecan with or without bevacizumab. Although there was no difference in outcome noted between the two chemotherapy regimens, the addition of bevacizumab led to a significant improvement in median OS, 17 months compared with 13.3 months in the chemotherapy alone arms (HR 0.71; 98% CI, 0.54 to 0.95; p = 0.004). Response rates were also higher for bevacizumab-containing arms (48% vs. 36%; p = 0.008). The benefit from bevacizumab was maintained in women with prior platinum exposure, recurrent/persistent disease, and responses were seen in previously irradiated fields. Toxicity, however, was increased by the addition of bevacizumab with an increased risk of fistula formation in gastrointestinal and genitourinary tracts (10.9% vs. 1%), grade 2 hypertension (25% vs. 2%), neutropenia (35% vs. 26%), and thromboembolism (8% vs. 1%). As a result of this study bevacizumab received a U.S. Food and Drug Administration label for the treatment of cervical cancer in combination with chemotherapy. This has become a new standard of care for women with cervical cancer in resource-rich populations, but expense precludes its use in most parts of the world.[70] A better understanding of the risk factors for fistulae development and identification of predictive biomarkers for response would help us to further refine the use of this drug by identifying the subgroups of women who may derive benefit while minimizing toxicity risk.

Antiangiogenic agents targeting other parts of the pathway have also been investigated in cervical cancer. Single agent, orally administered, multitargeted receptor tyrosine kinases inhibitors pazopanib (VEGFR 1, 2, and 3; PDGFR-α and β; and c-KIT) and sunitinib (VEGFR 1, 2 and 3; PDGFR, c-KIT, and FLT3) were studied in phase II trials. Sunitinib did not display sufficient activity to warrant further investigation and was associated with an unacceptably high (26%) rate of fistula formation.[92] In the second, larger study, 230 patients were randomly assigned to one of three arms: pazopanib alone, lapatinib (a tyrosine kinase targeting EGFR and HER2/neu) alone, or a combination of the two agents. Pazopanib improved PFS (HR 0.66; 90% CI, 0.48 to 0.91; p = 0.013) and OS (HR 0.67; 90% CI, 0.46 to 0.99; p = 0.045) compared with lapatinib alone. Median OS was 50.7 weeks compared with 39.1 week for pazopanib and lapatinib, respectively. Pazopanib alone was well tolerated, but the combination of the two drugs lacked efficacy and was associated with more serious adverse events.[93]

Clearly, targeting angiogenesis in cervical cancer has benefits in terms of efficacy, but patient selection is key and consideration of maintenance of QOL essential when considering future investigation of this therapeutic approach.

FIGURE 3. Rationale for Targeting Angiogenesis in Cervical Cancer
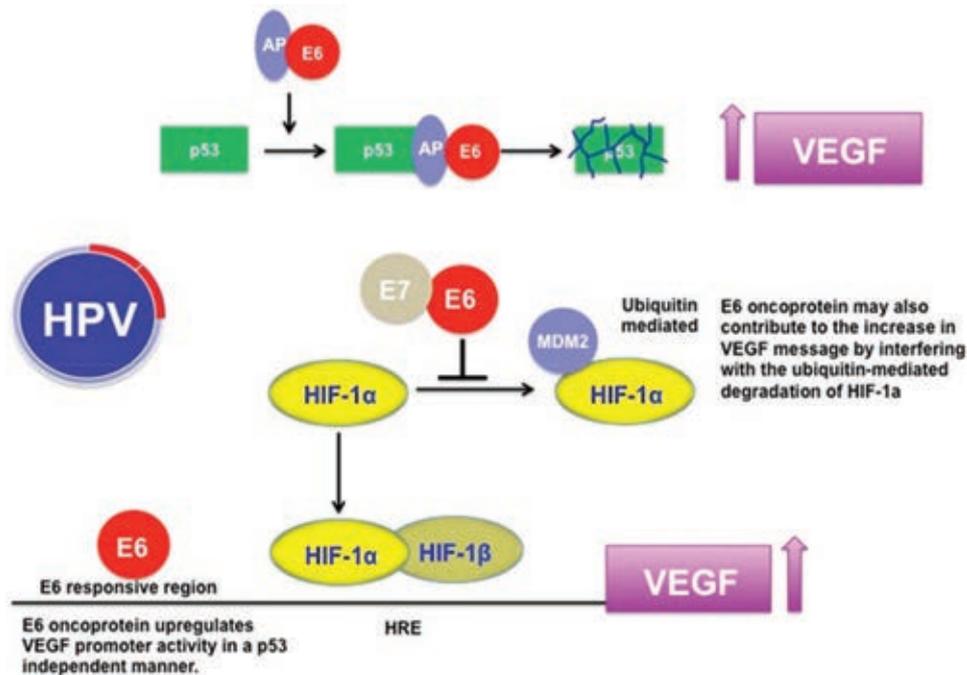
Abbreviations: TSP-1, thrombospondin-1; VEGF, vascular endothelial growth factor; HIF1α, hypoxia inducible factor 1α.

TABLE 1. Agents Currently under Investigation for the Treatment of Recurrent, Persistent, and Metastatic Cervical Cancer

Target	Phase of Study	Agent(s)	Clinical Trials No.
Immunotherapy			
CTLA	II	Ipilumimab	NCT01693783
PD-1	II	Nivolomab	NCT02257528
TiLs		TiLs	NCT01585428
T-cell immunotherapy	HPV16 only	T cells	NCT02280811
Pathway-Targeted Therapy			
RAS/ERK/PI3K/AKT/MTOR	II	Trametanib (MEK inhibitor)/GSK2141795 (AKT inhibitor)	NCT01958112
PI3K	II	BKM120	NCT01613677
RTK/Angiogenesis	II	Pazopanib/topotecan	NCT02348398
RTK/Angiogenesis	II	Carboplatin/paclitaxel ± nintedanib or placebo followed by maintenance	NCT02009579
HPV-Related Therapy			
HPV 16 and 18-positive cancer	II	VGX-3100 (plasmids encoding E6 and E7 protein)/INO-9012 (plasmid encoding interleukin 2) delivered via electroporation	NCT01693783
Therapeutic vaccine	I-II	ADXS11-001 high dose (therapeutic vaccine)	NCT02164461
	I-II		
	HPV 16 only	ISA101 (HPV 16 E6/E7 long peptides vaccine) with or without interferon alpha with carboplatin paclitaxel	NCT02128126
Cytotoxic Agents	II	Albumin-bound paclitaxel/nedaplatin	NCT01667211
	II	Eribulin mesylate	NCT0167818
Other			
Chromosome Region 1 Maintenance Protein	II	Selinexor	NCT02025985

Abbreviations: TiLs, tumor-infiltrating lymphocytes; HPV, human papillomavirus.
Studies are single arm unless otherwise indicated.

Targeting the EGFR

EGFR is expressed at moderate to high levels in cervical carcinoma. However, activating mutations are rare and studies evaluating the association of EGFR protein expression and prognosis in cervical cancer have yielded conflicting results.[95-96] Trials investigating the monoclonal antibody cetuximab, either alone or in combination with chemotherapy, failed to demonstrate sufficient clinical activity to warrant further investigation and reports of increased toxicity in combination with chemotherapy are concerning.[97-99] Clinical studies with the EGFR tyrosine kinase inhibitors gefitinib, erlotinib, and lapatinib were also disappointing.[100,101]

Molecular Profiling and Potential Therapeutic Targets

Our understanding of cervical cancer biology has focused around the role of HPV infection in the development of this disease.[102] The HPV oncoproteins E5, E6, and E7 are the primary viral factors responsible for initiation and progression of cervical cancer, and act largely by overcoming negative growth regulation by host cell proteins, including downstream effects that increase angiogenesis (Fig. 3).

Recent emerging data, however, are helping us to understand more about the genomic profile of cervical cancer. These data are helping to identify potentially "drugable targets" and thus new therapeutic approaches for investigation.

Activating mutations and amplification of *PIK3CA* (the gene encoding phosphoinositol-3-kinase) have been reported for some time, occurring in 23% to 36% of cervical cancer cases. Reports of somatic mutations in other genes including *PTEN*, *TP53*, *STK11*, and *KRAS* were also reported.[103-105] A more comprehensive analysis was published in 2014, which included whole-exome sequencing. Previously unknown somatic mutations were identified in 79 primary squamous cell cervical carcinomas (SCC), including recurrent substitutions in *MAPK* and inactivating mutations in *HLA-A*, *-B* and *B2M*, suggesting a role for immune evasion in cervical cancer (Table 1). HPV integration appeared to be a common mechanism for gene overexpression, including *ERBB2*, which also appears to occur as a result of somatic mutation and amplification.[106] A further paper from Wright et al focused on the differences between adenocarcinoma, which account for 10% to 20% of cervical cancers but have a worse prognosis, and SCC.[107] Although *PIK3CA* mutations and *PTEN* loss were observed in both histologic subtypes, *KRAS* mutations were detected only in adenocarcinomas (17.5% vs. 0%), and *EGFR* mutations only in SCC (0% vs. 7.5%).[108]

The prevalence of mutations within the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway, regardless of histologic subtype, make this an attractive therapeutic target in cervical cancer. An initial phase II study of the mTOR in-

hibitor temsirolimus for the treatment of women with metastatic or recurrent cervical cancer demonstrated limited activity.[109] However, further investigation of newer agents (such as PI3K inhibitors) alone or in combination are warranted, potentially in patient populations enriched for *PIK3CA* mutations. Other potential therapeutic directions include exploring MAPK1 inhibition or ERBB2 inhibition in patients with activating mutations and mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK) inhibitors in patients with *KRAS* mutations (extrapolating from the experience in low-grade serous ovarian cancer).

Immunotherapy

There is a strong rationale for investigating immunotherapy in cervical cancer given the host/HPV-induced immune evasion, which leads to persistent infection and carcinogenesis. Regulatory T cells are known to modulate the maintenance of an immunologically tolerant environment to HPV-associated preinvasive and malignant lesions.[110,111] Furthermore, the presence of tumor-infiltrating lymphocytes (TiLs) in tumor specimens has been associated with improved outcomes.[112,113] Currently, investigation of immunomodulating agents and strategies which either enhance the innate immune response to cervical cancer or repress immune-protective pathways are a very active area of cervical cancer research (Table 1). Upregulation of cytotoxic T lymphocyte-associated molecule-4 (CTLA-4) receptor on T lymphocytes is a negative regulator of T-cell activation. Ipilimumab is a fully human immunoglobulin (IgG1 kappa) that blocks CTLA-4. CTLA-4 blockade results in the expansion of activated T-cell clones directed at tumor epitopes, theoretically increasing immunovigilance and eradication of tumor cells.[114-116] Ipilimumab has demonstrated substantial clinical activity in patients with metastatic melanoma and is currently being investigated in two clinical trials enrolling women with advanced cervical cancer with results expected soon. (GOG 9929/NCT01711515; NCT01693783). A second attractive immunomodulatory strategy under investigation utilizes antibodies directed against another coinhibitory pathway on activated T-cells, the inhibitory receptor programmed cell death 1 (PD-1) and its ligand PD-L1. It remains to be seen if this approach will yield results in cervical cancer.[117] The use of bacterial vectors directed against E7 has been shown to induce tumor regression in preclinical models, and a phase II trial conducted in India with a live-attenuated *Listeria* monocytogenes vaccine suggests that this approach may be successful with further studies ongoing (GOG 265/NCT01266460).[118] Finally, patients with cervical cancer are being included in adoptive immunotherapy programs exploring the potential of TiLs harvested from patient tumor samples and then reinfused after immunodepletion (NCT01266460).

Targeting DNA Repair

Repair of DNA damage occurring in cells is essential for their survival. Therefore, inhibition of DNA repair following radio-

therapy is a potentially interesting strategy in cervical cancer. Furthermore, there are reports that a subgroup of cervical cancers may have defective homologous recombination as a result of epigenetic modification of the Fanconi anemia (FA) complementation group F (*FANCF*).[119,120] As a result, investigation of the poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors, which block base excision repair of single stranded DNA breaks, in cervical cancer a potentially interesting idea.[121] Other proposed strategies inhibiting the repair of DNA damage include inhibition of ribonucleotide reductase (RNR)[122,123] and agents which abrogate the G2/M arrest induced by radiation or chemotherapy, such as the Wee1 inhibitor MK1774 (NCT01076400).[124]

CHALLENGES IN CERVICAL CANCER RESEARCH

The majority of women affected globally by cervical cancer are unlikely to have access to trials or be able to afford new biologic therapies. Conducting clinical trials in patients with cervical cancer in the developed world is becoming increasingly challenging. Ironically, the falling incidence of cervical cancer in the developed world not only results in fewer women who are eligible for clinical trials, but may also result in a lack of interest by pharmaceutical companies to explore new agents in this patient population, despite the major mortality the disease causes worldwide. International collaboration is increasingly required to complete studies in a timely fashion, which, despite efforts in harmonization by organizations such as the GCIG, continue to pose substantial logistical barriers between countries. Within the United States, the patient demographic makes trial enrollment challenging.[125] The participation of ethnic minorities and medically underserved populations in clinical trials is critical to making progress. However, multiple well-documented factors account for disproportionally low enrollment rates among minority patients in clinical trials.[126-128] These include patients and their families being unaware of clinical trials, a fear of being "treated like a guinea pig,"[129-131] and the presence of mistrust of medical research and researchers among certain ethnic groups including American Indian, Asian American, and African American communities.[126,132,133] Furthermore, patients with cancer who are immigrants, live in rural areas, have a poor socioeconomic status, and work frequently cite practical concerns, including issues with transportation, family responsibilities, and out-of-pocket expenses as factors that inhibit their ability to participate in research.[126,134,135] It is imperative that clinical researchers of cervical cancer acknowledge these issues and reach out to our most vulnerable patients to provide assistance in helping them to become aware of all of their treatment options.

Given the relatively small numbers of patients available to enroll in clinical trials, it is essential that studies are rationally designed and based on biologically sound hypotheses. To limit the administrative burden and maximize participation, creative trial design is essential. Trial designs such as multiarm (or umbrella) or rolling phase II studies are essential if we are to investigate multiple agents in a time- and resource-efficient manner. Incorporation of translational substudies and functional imag-

ing studies will allow us to gain the maximum information from each trial. Commonality with other HPV-induced malignancies, such as cancers of the oropharynx and anal canal, suggest there might be underdeveloped routes of collaboration. Patients with cervical cancer may be eligible for studies requiring the presence of specific mutational profiles which are not limited to a particular cancer type.[125]

FINAL REMARKS

Much progress is still needed in the treatment of cervical cancer. It is important that we remember that the majority of women affected globally by cervical cancer are unlikely to be able to access new biologic therapies or have access to clinical trials. If we are to achieve maximum benefit for women with this disease, we need to reach out and form partnerships that allow us to raise the standards for all women. Costs must be considered in the development of new agents so that our results may be globally relevant, and advocacy is essential. Data from randomized trials exploring the role of adjuvant chemotherapy are expected soon that may change our approach to the front-line management of women with locally-advanced cervical cancer. However, the key to ensuring truly improved quality of care for patients is to recognize and identify patients who require supportive interventions both during and following therapy.

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GYNECOLOGIC CANCER

Managing Ovarian Cancer in the Older Woman: How to Best Select and Sequence Surgery and Chemotherapy for Optimal Outcome

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Epithelial Ovarian Cancer in Older Women: Defining the Best Management Approach

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OVERVIEW

Epithelial ovarian cancer is a cancer of older women. In fact, almost half of women diagnosed with ovarian cancer will be older than age 64, and 25% will be older than age 74. Therefore, it is crucial to examine the available data in older populations to optimize the therapeutic approach without negatively affecting the quality of life permanently. Unfortunately, little prospective data are available in this under-represented population of women. Although ovarian cancer traditionally has been approached with aggressive cytoreductive surgery, older patients may benefit from a less aggressive surgical approach and, in some cases, may be candidates for neoadjuvant chemotherapy followed by an interval cytoreduction. Modalities do exist for assessing an older woman's ability to tolerate surgery and chemotherapy, and these tools should be familiar to clinicians who are caring for this population of women in making treatment decisions. Ongoing planned trials to evaluate pretreatment assessment for older patients will provide objective, feasible, clinical tools for applying our treatment-based knowledge. Future trials of both surgery and chemotherapy, including a focus on the sequence of these two treatment modalities, are crucial to guide decision making in this vulnerable population and to improve outcomes for all.

Close to half (45%) of women diagnosed with ovarian cancer will be older than age 64, and 25% will be older than age 74 (20.7%, age 65 to 74; 16.6%, age 75 to 84; and 8.1%, older than age 84).[1] The mean age at diagnosis of ovarian cancer is 63 years.[1,2] In addition, the percentage of older women with ovarian cancer is expected to increase in the coming decades as our population ages and life expectancy improves.[3,4] Unfortunately, as the age of the patients increases, cancer outcomes steadily worsen. One report showed age-standardized relative survival rates at 1 year of 57% for women age 65 to 69, 43% to 45% for those age 70 to 79, and 25% to 33% for those age 80 to 99.[5] There have been various theories put forward to account for the decreased survival in older women, including the following: (1) more aggressive tumor biology, including higher grade and more advanced stage, (2) inherent resistance to chemotherapy, (3) individual patient factors, such as multiple concurrent medical problems, functional decline, and malnutrition leading to greater anticipated treatment toxicity, and (4) physician and health care biases toward older adults that lead to inadequate surgery, and suboptimal chemotherapy.[6]

To improve the outcomes of older women with ovarian cancer, we need to develop better decision aids to discriminate those patients who will and will not tolerate standard cytoreductive surgery (CRS) and chemotherapy. Our trials cannot continue to focus exclusively on younger, fit women and the healthiest subsection of older women. In the South-west Oncology Group (SWOG) analysis of data on 16,396 patients enrolled in 164 trials during the 1990s, patients older than age 65 accounted for only 30% of all included patients.[7] Similarly, in a recent Surveillance, Epidemiology, and End Results (SEER) survey, only 9% of patients older than age 75 who had cancer were included in clinical trials of new therapies.[8] With a focus on improving under-represented populations, cooperative groups in the U.S. (Elderly Working Group in the NRG Gynecologic Oncology Group [GOG]) and Europe (Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens, GINECO) are developing trials specific for older women with gynecologic cancer.

In this review, we will discuss currently available data regarding results of surgery and chemotherapy in the older woman with ovarian cancer as well as review geriatric assessment (GA) tools being developed to aid decision making regarding both surgical and chemotherapeutic interventions.

Ovarian Cancer Surgery in Older Women

The data for surgery in epithelial ovarian cancer (EOC), although retrospective, is clear: patients with advanced (stages III to IV disease) will experience an improved overall survival if they undergo an optimal CRS.[9,10] The meaning of optimal has changed over time, with an accepted current definition in the platinum era of less than 1 cm of residual disease.[11] Most recently, it has been suggested that no visible residual should be the goal of a cytoreductive surgery. The improved survival

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associated with optimal CRS has been confirmed in recent prospective, randomized trials of chemotherapy.[12-14]

There remains, however, controversy regarding the role of neoadjuvant chemotherapy (NACT) followed by an interval cytoreduction (iCRS) as a primary strategy for the treatment of ovarian cancer. The aggressive surgical effort that is required for an optimal primary surgery may result in postoperative morbidity; the interval surgery associated with NACT may be less extensive and, therefore, better tolerated.[15] The idea that all patients, regardless of comorbidities, should be approached with a primary surgical effort has transformed into consideration of NACT with iCRS for those patients who may not tolerate an up-front maximal surgical effort.

Risk factors for postoperative morbidity after primary surgery for ovarian cancer have been identified. These include older age (older than age 75), poor performance status (PS), low serum albumin, the presence of ascites, and high preoperative CA 125.[16] Thus, age becomes an important factor in determining the best first therapy for women who present with advanced disease when surgery and the timing of surgery are being considered.

Older studies noted that older women with ovarian cancer have a worse prognosis than younger women and suggested that this worse prognosis may be due to a less aggressive surgical approach to the disease. The American Cancer Society analysis from Hightower et al,[17] for example, noted a significant reduction in survival for patients older than age 80 compared with their younger counterparts; this decrease was attributed to a less aggressive surgical approach.[17] The older women were more likely to see a general surgeon rather than a gynecologic oncologist for their surgery and also were more likely to have a suboptimal CRS performed. In addition, older patients in this series were less likely to receive adjuvant chemotherapy (42% vs. 69%, p < 0.0001). The finding that older women are less likely to have an aggressive surgical effort also has been confirmed by other series.[18-21] In part, this finding may be due to the observation that women older than age 70 are less likely to be seen by a gynecologic oncologist.[22]

More recent studies consist of a series of single tertiary institution findings, reported by gynecologic oncologists, that are retrospective in nature and consequently affected by selection bias. The majority of these studies suggest that older women tolerate aggressive surgical effort well, with a conse-

quent similar overall survival to their younger counterparts.[23-25] However, a select few have noted significant morbidity in the cohort of very older ages (greater than 80).[16,26,27] In particular, the report from Oklahoma noted a significant rate of death before hospital discharge and within 30 days of surgery in women older than age 80 who underwent primary cytoreduction.[26] Although the authors were able to achieve a 74% rate of optimal cytoreduction in this group of patients (defined in this study as less than 1 cm of disease remaining), postoperative complications were common. In addition, and perhaps more significant, 13% were unable to receive adjuvant chemotherapy and, of those who were treated, only 57% completed more than three cycles.

Population-based studies have confirmed age as an independent risk factor for surgical morbidity. In the SEER analysis reported by Thrall et al,[28] advancing age was associated with a significant increase in 30-day mortality. Among their sample of 5,475 patients, patients older than age 85 had five times the mortality risk as those age 65 to 69 (17.52% vs. 3.19%, respectively). When age was evaluated as a continuous variable, each year over age 65 was associated with a 7.5% increase in the risk of 30-day mortality. The authors performed further risk modeling, including stage and comorbidity, and found that women at the highest risk (more than 10%) for 30-day mortality after CRS were those older than age 75 with stage IV disease or those older than age 75 with stage III disease and a comorbidity score of +1.[28] Another study using data from the Nationwide Inpatient Sample registry of patients admitted for ovarian cancer surgery also found that perioperative complications increased with age.[29] Among the 28,651 patients included, those patients younger than age 50 had a 17.1% complication rate compared with rates of 29.7% in patients age 70 to 79 and 31.5% in patients older than age 80. Discharge to a facility also increased with age, from only 1.0% of patients younger than age 50 to 14.0% of patients age 70 to 79 and 33.3% of patients older than age 80. In the multivariate analysis, age, number of medical comorbidities, and number of radical procedures performed were the most important predictors of morbidity and mortality.

Finally, Wright et al[30] reported SEER data for women age 65 years or older, this time with the primary goal of assessing reception of adjuvant therapy after primary surgery.[30] In a multivariate model, older patients and those with comorbidities, mucinous tumors, and stage IV cancers were more likely to not receive chemotherapy after surgery, and age remained a predictor of delay of initiation of chemotherapy.[30] These studies are shown in Fig. 1.

Likely, age alone cannot suffice as a measure of postoperative surgical morbidity and mortality. Instead, a combination of factors should be used to identify a group of patients for whom an up-front surgery will not be of benefit. The ability to assess who is fit enough to undergo aggressive CRS followed by chemotherapy and who should be offered an alternative pathway, such as NACT and iCRS or primary chemotherapy alone, is an unmet need. In the study from Aletti et al,[16] when tumor distribution, age, and nutritional status were combined, the authors were able to identify a subgroup

KEY POINTS

- Almost half of women with ovarian cancer are older than age 64 years, and 25% are older than 74 years.
- Older patients may benefit from a less aggressive surgical approach and, in appropriate cases, may be candidates for neoadjuvant chemotherapy.
- Validated modalities exist for assessing an older woman's ability to tolerate surgery and chemotherapy, and these tools should be utilized when caring for this population in making treatment decisions.

FIGURE 1. Risks of Cytoreductive Surgery in Advanced Ovarian Cancer Increase with Age

Complication	Younger than Age 50	Age 50 to 59	Age 60 to 69	Age 70 to 79	Age 80 and Older
30-Day Postoperative Mortality[28]			4.6%*	Age 70-74: 5.4% Age 70-79: 9%	Age 80-84: 12% Age 85+: 21%
Postoperative Morbidity[29]	17.1%	20.2%	25.5%	29.7%	31.5%
Nontraditional Discharge[29]	< 1%	1.8%	4.4%	14%	33.3%
Receipt of Chemotherapy Postoperatively Chemo Omitted[30] Chemo Delayed > 6 wk[30] Chemo Delayed > 12 wk[30]			12.9%* 20% 3%	Age 70-74: 23% Age 75-79: 21% 24-25% 2-5%	42.8% 29% 8%

* Data for age > 65.

of patients for whom the benefits of an aggressive up-front surgery did not outweigh the risks.[16] In addition, in this group of patients, aggressive surgery did not result in improved overall survival.

Further prospective study is warranted to identify those women for whom primary CRS is not indicated. If we use a generalized preoperative assessment for all patients, we may exclude many who might benefit from aggressive primary CRS. However, by not validating a preoperative tool in this vulnerable population, we risk excess morbidity and mortality in those patients with too little reserve to tolerate primary CRS followed by chemotherapy.

OVARIAN CANCER CHEMOTHERAPY IN OLDER WOMEN
Timing of Chemotherapy: NACT

NACT is the delivery of chemotherapy before a CRS. NACT use is gaining popularity in both the United States and Europe, particularly for older and frail patients. By shrinking cancer before surgery, several reports suggest that NACT increases the chance of an optimal CRS (defined as no gross residual disease postsurgery) with less surgical morbidity and no significant effect on survival.[31,32]

The only published prospective, randomized study of NACT versus primary CRS followed by adjuvant chemotherapy is study 55971 from the European Organization for Research and Treatment of Cancer (EORTC).[31] The 632 patients with newly diagnosed stage IIIC or IV EOC were randomly assigned to either primary CRS followed by six cycles of platinum-based chemotherapy or to three cycles of NACT platinum-based followed by an iCRS followed by an additional three cycles of platinum-based chemotherapy. The two cohorts had similar baseline characteristics (age, PS, histology type, grade, and stage). The median ages were 62 (range, ages 25 to 86) in the primary surgery group and 63 (range, ages 33 to 81) in the NACT group. No subgroup analysis was reported based on older age.

NACT was not inferior to primary surgery; the median overall survival times were 29 months in the primary debulking group and 30 months in those assigned to NACT. Although outcomes were equivalent, the median survival in each arm was relatively short, which suggests that the trial may have selected for a poor prognostic group of patients. The authors found that one of the main predictors of survival was no gross residual disease, so the question of NACT versus primary CRS remains controversial as it pertains to those patients for whom no gross residual disease is a reasonable expectation.

The CHORUS trial is another randomized, phase III trial with identical eligibility criteria to that of EORTC 55971.[33] This study has only been reported in abstract form, but the primary endpoint of overall survival was not statistically different, at 22.8 versus 24.5 months for the pCRS and iCRS groups, respectively. These two studies were meant to be evaluated together; with combined data for this selected population, the overall estimate of the hazard ratio (HR) was 0.93 (95% CI, 0.81 to 1.06).

Several things are notable about these studies compared with the GOG studies, not specific to older women, that were described previously.[34] First, the median age of the patients enrolled in EORTC 55971 and CHORUS were almost a decade older than those patients enrolled in the GOG studies. On the EORTC and CHORUS studies, 20% to 32% of patients had a PS of 2 to 3 compared with 8.5% of patients on the prior GOG studies, and approximately 25% of patients on the EORTC and CHORUS studies had stage IV disease compared with none in the prior GOG studies cited, which makes this a highly selected, poor-prognosis group of patients (Fig. 2).[33,34]

Older women, particularly those with high comorbidities and frailty, are at the highest risk of surgical morbidity and may be the most appropriate candidates for NACT. Although each patient plan must be individualized, these criteria are reasonable to use as guidelines for an NACT approach.

FIGURE 2. Surgery for Patients with Ovarian Cancer[31,44,69]

	AGO-OVAR	GOG	EORTC 55971 pCRS iCRS	
Suboptimal > 1 cm	29.6 mos	35.0 mos	26 mos	25
Gross optimal ≤ 1 cm	36.2 mos	42.4 mos	32 mos	27
NGR	99 mos	71.9 mos	45 mos	38
Age	58.9	57	62-63	
PS	0 38% 2 10.4%	0 41% 2 8.5%	0 45% 2-3 32%	
Stage	II 8.9% III 74% IV 17%	III 100%	IIIc 76.5 -75.7% IV 22.9- 24.3%	

Timing of Chemotherapy: After Primary Surgery

EOC is one of the most chemotherapy-sensitive diseases, with high initial response rates. The standard of care has evolved into taxane and platinum-based regimens that vary in schedule and route of administration. However, the studies that established these standards of care contained few older patients (here defined as age 70 or older), and the vast majority of those included would have been the most fit and had a high PS. For example, in GOG 158, which established paclitaxel and carboplatin as a standard of care, and GOG 172, which established intraperitoneal cisplatin and paclitaxel-based therapy as a standard for patients after optimal cytoreduction, only 12% of patients enrolled were older than age 70.[13,35] Similarly, both GOG 218 and ICON 7, which evaluated the addition of bevacizumab to every-21-day paclitaxel and carboplatin, enrolled 23% and 10%, respectively, older than age 70.[36,37] GOG 182, one of the largest randomized trials in EOC completed, with more than 4,000 enrolled patients, included 23% who were older than age 70.[14] Although no subset analyses were done in the older population of patients in these trials, a post hoc analysis of the 620 patients age 70 or older enrolled in GOG 182 found that this group had a poorer PS, lower chemotherapy completion rates, increased toxicities (neuropathy and cytopenias) and an 8-month shorter overall survival after adjusting for other prognostic factors.[38]

These adverse outcomes, among highly selected older patients who were deemed fit enough to enroll in a prospective clinical trial, are significant and reflect the difficulty in assessing reserve for treatment in an older population. The uncertainty surrounding how much an older woman can tolerate, combined with competing comorbid and social conditions may explain the low percentage of older women receiving standard of care chemotherapy for ovarian cancer. In one SEER review of the use of chemotherapy in advanced EOC, the odds of chemotherapy being administered dropped with age compared with the reference group of ages 65 to 69.[39] For example, women age 75 to 79 had a odds ratio (OR) of 0.65, women age 80 to 84 had an OR of 0.24, and women age 85 and older had an OR of 0.12.[39] A second SEER analysis found that the women at greatest risk of incomplete chemotherapy (either not given or received an incomplete course) were those older than age 76 (OR, 1.64) and/or two or more medical comorbidities.[40]

Designated clinical trials for older women and PS–challenged women have been completed outside the United States. The first designated trial for this population (GOG 273) was completed in the United States and presented in abstract form in 2014, giving us useful guidelines on the selection of the best therapies for these patients.[41]

Front-line chemotherapy options. Because of concerns related to excess toxicity among older women, investigations have focused on improving tolerance while maintaining efficacy. There are three main foci of investigation: (1) initial dose modifications, (2) variations in scheduling, and (3) timing (neoadjuvant vs. primary chemotherapy). NACT is addressed above and will not be readdressed in this section.

Initial dose modification. In 1997, the GINECO group in France launched a dedicated older women ovarian cancer (EWOC) program. Between 1998 and 2003, two prospective studies were conducted to assess the tolerability of the current standard platinum-based chemotherapy regimens. Both studies enrolled women age 70 or older, with liberal inclusion

criteria, and a baseline GA was performed. In the first study (EWOC 1), 83 patients (median age, 76) with stage III/IV EOC received carboplatin (area under the curve [AUC] 5) and cyclophosphamide (600 mg/m^2) in combination (i.e., CC) on day one every 28 days for six cycles. The rate of the completion of all six cycles of the CC regimen was 72%, with minimal toxicities.[42] Moreover, GA predicted toxicity and overall survival. In the multivariate analysis, three factors appeared to have a prognostic value of toxicity: symptoms of depression at baseline (p = 0.006), dependence (p = 0.048), and PS of 2 or greater (p = 0.026). Independent prognostic factors identified for overall survival (Cox model) were depression (p = 0.003), International Federation of Gynecology and Obstetrics (FIGO) stage IV (p = 0.007), and more than six medications per day (p = 0.043). The second study (EWOC 2) assessed the feasibility of carboplatin (AUC 5) with paclitaxel (175 mg/m^2) (CP) once every 3 weeks for six cycles in 75 older patients. The feasibility of completing all six cycles for patients receiving CP was 68%.[43]

These two studies were pooled in a retrospective, multivariate analysis (EWOC 1 plus EWOC2) to assess predictive factors of survival.[43] Patients in the EWOC 2 study appeared to be younger and had better PS than those in the EWOC 1 study, which indicated a selection bias because of a concern that the CP regimen could be associated with higher toxicity. The CP regimen had more hematologic (grade 3 to 4) and neurologic toxicities. Despite the inclusion of a higher proportion of patients with optimal CRS (1 cm or less of residual disease) in the CP regimen (40% vs. 21% in the CC regimen), the survival curves were similar. Predictive factors of poor prognosis were advanced age, depression symptoms at baseline, and FIGO stage IV. The use of paclitaxel was found to be an independent factor for poor survival (HR = 2.42, p = 0.001).

However, given that this was a small, nonrandomized study, the validity of this finding is unclear. GOG 273 may address this issue when survival analyses are available. This study enrolled women older than age 70 with newly diagnosed EOC and allowed physicians to select treatment either with every-3-week paclitaxel (135 mg/m^2) and carboplatin (AUC 5) plus pegfilgrastim support or with every-3-week carboplatin alone (AUC 5). The primary endpoint was the ability of independent activities of daily living (IADL) score to predict completion of four cycles of chemotherapy.

This study enrolled 153 women onto the combination arm and 59 onto the single-agent carboplatin arm. The study was not randomized, so it is not unexpected that the women in the single-agent arm were older (median age, 83 vs. 77), had a lower PS (PS of 2 to 3: 37% vs. 11%), were more likely to receive NACT (58% vs. 49%), and were less likely to complete all four cycles without a dose reduction or a more than 7-day delay (54% vs. 82%). However, overall completion of four cycles was high in both arms (92% and 75% in the combination and single-agent arms, respectively). Although the primary endpoint of the ability of IADL to predict completion of four cycles of chemotherapy was not met, patients in both arms reported improved quality of life, social activity, and function

(i.e., activities of daily living [ADL]) with increasing cycles of chemotherapy.[41]

The EWOC 3 study evaluated the use of single-agent carboplatin AUC 5 in a highly selected, frail population. This study was used to validate the geriatric vulnerability score (GVS) developed during evaluation of the baseline GAs done for EWOC 1 and 2. The GVS will be discussed more in the section on GAs later in this chapter.[44]

Variations in scheduling. The MITO-5 (Multicenter Italian Trial in Ovarian cancer) phase II study assessed the tolerability of a weekly combination of carboplatin (AUC 2) plus paclitaxel (60 mg/m^2) on days 1, 8, and 15, every 4 weeks for six cycles in a small trial of 26 patients age 70 or older with stage IC to IV disease and performance status up to or less than PS 2.[45] In this study, 54% patients had at least two comorbidities and high functional dependency (ADL, 31%; IADL, 69%). The RECIST response rate was 38.5%, and the median overall survival was 32.0 months. Toxicity was low; 23 patients (89%) were treated without any defined-as-unacceptable toxicity (primary study endpoint).

The larger randomized, phase III trial (MITO-7) evaluated the same weekly regimen used in MITO-5 versus standard carboplatin (AUC 6) with paclitaxel (175 mg/m^2) every 3 weeks in women with newly diagnosed EOC.[46] Although this trial was not specifically for older women, it did confirm the possible advantages of the weekly regimen, because it was associated with better quality of life scores and lower toxicity, including lower incidence of neuropathy worse than grade 2 and fewer incidences of grade 3 to 4 hematologic toxicity. There was no survival advantage to the weekly regimen but no decrement either (median progression-free survival, 17.3 vs. 18.3 months), which supports this regimen as an alternative to every-21-day paclitaxel and carboplatin, especially among more vulnerable patients.

Because of the interest in weekly dosing generated by this and other phase III trials, GOG 273 added a weekly arm to evaluate carboplatin AUC 5 with weekly paclitaxel 60 mg/m^2. For this arm of the trial, the primary endpoint is to determine if an eight-point GA score could predict the ability to tolerate chemotherapy.[47] This study has completed enrollment, and follow-up care is ongoing. In France, the most recent EWOC trial is enrolling as well. This randomized, phase II trial (NCT02001272) plans to enroll 264 patients, and treatment arms will encompass both initial dose modification strategies and weekly strategies (single-agent carboplatin, combination carboplatin and paclitaxel, and a weekly paclitaxel and carboplatin arm, similar to MITO-7). Eligibility for EWOC is defined by a GVS score greater than 3, again selecting for a very vulnerable population of older patients. A summary of clinical trials performed in the older patient with ovarian cancer is provided in Fig. 3.

Is intraperitoneal chemotherapy a consideration for the older patient? Cisplatin-based intraperitoneal chemotherapy has a demonstrated significant survival benefit for patients with an optimal CRS for stage III ovarian cancer and is a standard of

FIGURE 3. Chemotherapy Trials in the Older Patients

Study	Inclusion	Agents Used	Overall Survival (Median Months)	Discovery
EWOC-1 (83 patients, phase II, single arm)	> 70, stage III/IV Enrolled: (Age 70-90) Phase ≥ 2: 44% Stage IV: 24%	Carboplatin AUC 5 + cyclophosphamide 600 mg/m2 q 28 days for 6 days	21.6	OS associated with: (1) depression (p = 0.003), (2) stage IV (p = 0.007), (3) > 6 medications/day (p = 0.043). Toxicity associated with: (1) depression (p=0.006), (2) dependence of ADL or IADL (p=0.048), (3) PS ≥ 2.
EWOC-2 (75 patients, phase II, single arm)	Age > 70, stage III/IV Enrolled: (Age 70-89) Phase ≥ 2: 26% Stage IV: 22%	Carboplatin AUC 5 + paclitaxel q 21 days	25.9	OS associated with the HADS > 15*
EWOC-3 (111 patients, phase II, single arm)	Age > 70, stage III/IV	Carboplatin AUC 5	17.4	Validated the GVS**
MITO 5 (phase II, single arm)	Age ≥ 70, stage IC-IV	Carboplatin AUC 2 + paclitaxel 60mg/m2 day 1, 8, 15 every 28 days	32	89% of patients were treated without protocol defined unacceptable toxicity
GOG 273 (212 patients; includes only arms I and 2; phase II; multi-arm; not randomized)	Age ≥ 70, stage IC-IV	Physician choice: (1) carboplatin AUC 5 + paclitaxel 135mg/m2 + G-CSF q 21 days, (2) carboplatin AUC 5 q 21 days, (3) carboplatin AUC 5 every 21 days + paclitaxel 60mg/m2 day 1, 8, 15 (results for this arm have not been presented)		Endpoint was trying to correlate IADLs with ability to complete 4 cycles of chemotherapy without delay >7 days or dose modification. Arm 1: 82% completed without delay or dose mod. Arm 2: 54% completed without delay or dose mod. Patients in both arms reported improved quality of life, social activity, and ADL with increasing cycles of chemotherapy.

* HADS (Hospital Anxiety and Depression Scale).
** GVS (Geriatric Vulnerability Scale).

care at many U.S. cancer centers. Despite growing acceptance of its superior survival advantages, several concerns remain, including technical difficulties (intraperitoneal catheter placement and complications) and increased toxicities (renal dysfunction, neuropathy, hearing loss). In GOG 172, 39% of the 205 women who received intraperitoneal cisplatin/paclitaxel were older: 26% were age 61 to 70), 12% were age 71 to 80, and 1% were older than age 80.[35] Their functional status was good (92% with a GOG PS of 0 to 1). Regardless of age, less than 50% of all patients were able to complete four or more cycles of the intraperitoneal regimen because of toxicity.

How does an oncologist apply these results to their older population? First, the major limitation to the study was that patients received intraperitoneal cisplatin. By age 70, renal function may have declined by as much as 40%, and this reduction in glomerular filtration rate may lead to enhanced toxicity of drugs, particularly those with significant renal excretion, such as cisplatin. On GOG 172, patients were re-

quired to have a serum creatinine less than 1.2 mg/dL; however, creatinine clearance is a more sensitive marker for renal dysfunction and should be used.[48] The second limitation was the use of paclitaxel, because its drug clearance declines with age and its toxicities, such as neuropathy and cytopenias, heighten.[49] Even with the overall survival benefit demonstrated with intraperitoneal therapy, widespread adoption of this modality has been slow secondary to the limitations discussed.

If intraperitoneal chemotherapy is offered as an option to older women, one needs to carefully select patients with good functional status, adequate kidney and hearing function, and an understanding that toxicities may arise earlier in the course of treatment compared with intravenous chemotherapy alone.

Chemotherapy for recurrent disease. Treatment for recurrent ovarian cancer is divided into relapse at 6 months or fewer since the last platinum-containing chemotherapy administration, as platinum resistant, and at greater than 6 months as platinum sensitive. For platinum-sensitive disease, trials show the survival advantage of a doublet combination with carboplatin and either paclitaxel, liposomal doxorubicin, or gemcitabine.[50,51] The combination of carboplatin and paclitaxel (in CALYPSO) was significantly associated with a higher incidence of neurologic toxicity (neuropathy greater than grade 2) among patients older than age 70 (25% vs. 16%, respectively; p = 0.006).[52] Although the proportion of older patients (median age, 73) comprised only 16% of the study population, the prevention of severe neurologic toxicity would advocate for the use of pegylated liposomal doxorubicin rather than paclitaxel in older women.

For platinum-resistant disease, chemotherapy is typically given as single agent, with responses from 10% to 25% and a median duration of 4 to 8 months. Common options include liposomal doxorubicin, topotecan, gemcitabine, weekly paclitaxel, and single-agent bevacizumab.[53] Unfortunately, few studies have been reported in older patients with ovarian cancer. Based on extensive studies from lung and breast cancer in older patients, most of these single-agent drugs are well tolerated.[54,55] Gronlund et al[56] described their experience with topotecan (1 mg/m^2 over 5 days) in 57 older patients with platinum-resistant ovarian cancer and found no significant differences in the toxicity profile or response between an older (older than age 65) or younger (younger than 65) cohort.[56] PS was a better predictor of response and survival in both cohorts. Currently, most oncologists use liposomal doxorubicin or weekly topotecan for older patients with platinum-resistance, given its improved toxicity profile.[57,58] The recent publication of the AURELIA trial and the subsequent U.S. Food and Drug Administration (FDA) label for bevacizumab 10 mg/kg every 2 weeks with either pegylated liposomal doxorubicin (PLD) 40 mg/m^2, weekly paclitaxel 80 mg/m^2 for four doses, or topotecan 4 mg/m^2 weekly for three doses has created yet another option for the platinum-resistant population. The median age of patients on the chemotherapy/bevacizumab arm was 62, but the range was ages 25 to 80.[59] There was criticism of this study because of the lack of a bevacizumab-alone arm, which is considered an effective agent but is not FDA approved for this indication on the basis of only phase II data.[60] Hypertension and arterial thrombosis risk may be heightened in an older patient who has more comorbidities. Previously reported high bowel perforation rates (as high as 11%) have been greatly diminished, and recent data from a prospective, phase III trial demonstrated a 2.8% rate of perforation among those treated with bevacizumab compared with 1.2% in those treated without. Age was not mentioned as a risk for bowel perforation in this study.[36]

Because these chemotherapy options offer primarily palliation, many argue for a focus on better supportive measures rather than more chemotherapy. In one study, there was a significant cost difference, with no appreciable improvement in survival in a comparison of patients with ovarian cancer treated aggressively with chemotherapy with those enrolled in hospice at the final months of their life. The authors suggest that earlier hospice enrollment is beneficial, particularly in the older frail patients who have poor prognoses.[61]

Assessment of the Older Woman for Ovarian Cancer Treatment: Making Data Driven Decisions

Geriatric assessment (GA) provides information about a patient's functional status (i.e., ability to live independently at home and in the community), comorbid medical conditions, cognition, psychologic status, social functioning support, and nutritional status. In the cancer setting, several studies have demonstrated the predictive value of GA for estimating the risk of severe toxicity from chemotherapy.[47,62,63] A validated instrument for assessment specifically for the older patient with ovarian cancer does not yet exist. There are several assessments used in the older adult with cancer (Fig. 4), but further prospective studies are imperative to remove the guesswork from assessing a patient's fitness for surgery or chemotherapy.

Presurgery assessment. Traditional models of preoperative assessment (e.g., Lee, Eagle, American Society of Anesthesiologists) do not consider the multisystem assessment needed to evaluate an older patient. The Preoperative Assessment of Cancer in the Elderly (PACE) tool was developed to combine elements of the comprehensive GA with surgical risk assessment tools in an older cancer population, although no gynecologic patients were included (Fig. 4). The authors found no significant association of age with postoperative complications. However, 30-day morbidity was predicted by IADL (i.e., more complex activities, such as managing finances and shopping), moderate to severely elevated scores on the Brief Fatigue Inventory (BFI), and abnormal PS. An extended hospital stay was predicted by lower scores in ADL (i.e., basic activities, such as eating, bathing, dressing), IADL, and worse PS.[64,65]

A position paper was released in 2012 by the American College of Surgeons that outlined the best practices for optimal preoperative assessment of the geriatric patient with a

FIGURE 4. Geriatric Assessment in Older Adults with Cancer

	PACE: Preoperative assessment of cancer in elderly.	CARG: Cancer and aging research group study	NRG-CC001: Preoperative assessment study	GOG273: Geriatric assessment score	GVS: Geriatrics vulnerability scale
Setting	Preoperative	Prechemotherapy	Preoperative	Prechemotherapy	Prechemotherapy
Cancer Type	Solid tumor	Solid tumor	Ovarian and endometrial serous cancer	Ovarian cancer	Ovarian cancer
Population	≥65yo	≥65yo	≥70yo	≥70yo	≥70yo
Variables	1) Mini-mental state inventory 2) Activities of daily living (ADL) 3) Instrumental activities of daily living (IADL) 4) Global depression scale (GDS) 5) Brief fatigue inventory (BFI) 6) Performance status (PS) 7) ASA 8) Satariano's index of co-morbidities	If yes to below— a graded value is added to a toxicity score: 1) Age ≥ 72 2) Cancer type (GI or GU) 3) Standard dosing 4) Poly-chemotherapy 5) Anemia 6) Renal dysfunction (CrCl b 34 mL/min) 7) Decreased hearing 8) Falls in last 6 months 9) Assistance with taking medication 10) Limited walking 1 block 11) Decreased social activity	Measures to be collected: 1) Function (ADL, IADL, PS, Fall Hx) 2) Comorbidity (Physical Health Section of OARS) 3) Psychological (Mental Health Inventory-17) 4) Social Activity/Support— MOS Surveys 5) Brief Fatigue Inventory 6) Nutrition (BMI, weight loss) 7) Medication list	Measures to be collected: 1) Function (ADL, IADL, PS) 2) Comorbidity (Charlson Score, Hearing Loss, Fall Hx) 3) FACT-O 4) FACT/GOG-NTX-4 5) Nutrition (BMI, weight Loss)	If yes to below— a graded value is added to a toxicity score (GVS): 1) Low albumin 2) Low ADL 3) Low IADL 4) Lymphopenia 5) High Hospital Anxiety and Depression (HADS) score
Conclusion	1) IADL, BFI and PS predicts 30 day morbidity 2) ADL, IADL and PS associated with extended hospital stay.	A toxicity score ranging from 0 to 23 identified patients at greatest risk of grade 3–5 chemotherapy toxicity.	Accrual underway	Final report pending	Accrual underway.

standard checklist.[66] Timed Up & Go has been reported to predict 30-day surgical morbidity in patients age 70 or older who were undergoing cancer surgery (61% involved laparotomy). This was part of the PREOP study that was designed to assess a number of different presurgical assessments in older patients who had a variety of cancers and were undergoing a variety of different operations.[67]

A unique multicenter study (NRG-CC002) under accrual is focused exclusively on women older than age 70 at the time of diagnosis of a gynecologic cancer (advanced ovarian or en-

dometrial serous cancer). Before surgery or NACT, geriatric measures will be collected, to include the following: (1) function (ADL, IADL, PS, fall history), (2) comorbidity (physical health section of Older Americans Resources and Services), (3) psychologic (Mental Health Inventory-17), (4) social activity/support (Medical Outcomes Study survey), (5) nutrition (body mass index, weight loss), (6) Brief Fatigue Inventory, and (7) medications. A risk score will be calculated to determine its ability to predict major postoperative complications.

Prechemotherapy assessment. A simple and short screening test to assess toxicity risk for older vulnerable women with ovarian cancer undergoing chemotherapy is clearly needed, and a variety have been or are being tested (Fig. 4). Examples of short surveys used in various cancers are the Vulnerable Elders Survey (VES-13) and the Cancer and Aging Research Group (CARG)–GA and toxicity score. VES-13 is a self-administered survey that consists of one question for age and 12 additional questions that assess self- rated health, functional capacity, and physical performance. CARG-GA is a feasible assessment (mean time to completion is 27 minutes, mostly self administered) with an 11-variable toxicity score (Fig. 4). The score predicted grade 3 to 5 chemotherapy toxicity far better than PS.[47] The CARG study did include a small proportion of women who had ovarian cancer (50 patients, 10%), and a retrospective subgroup analysis showed that grades 3 to 5 toxicity occurred in 19 patients (37%). Abnor-

mal CA125 was associated with assistance with IADL, low PS, chemotherapy toxicity, and dose reductions.[68]

The French GINECO group has developed a GVS from a series of up-front trials in older women with ovarian cancer. The GVS includes the high-risk variables of low albumin (less than 35 g/L), low ADL score (less than 6), low IADL score (less than 25), lymphopenia (less than 1G/L), and a high hospital anxiety and depression (HADS) score (greater than 14).[44] Women with a high GVS score (3 or greater) had a worse overall survival (11.5 vs. 21.7 months; HR, 2.94; p < 0.001), experienced a lower rate of chemotherapy completion (65% vs. 82%; OR = 0.41; p = 0.04), had higher incidences of severe adverse events (53% vs. 29%; OR = 2.8; p = 0.009), and more unplanned hospitalizations (53% vs. 30%; OR = 2.6, p = 0.02). The use of the GVS appears helpful in selecting those at greatest risk; validation studies with larger cohorts are underway.

CONCLUSION

As designated treatment trials for the older and performance-challenged woman with ovarian cancer increase, our understanding of and ability to discern best practices for treatment planning increase. In addition, the ongoing planned trials evaluating pretreatment assessment for older patients will provide objective, feasible, clinical tools for applying our treatment-based knowledge. These important works will hopefully eliminate much of the gestalt decision making in this potentially vulnerable population and improve outcomes for all.

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GYNECOLOGIC CANCER

Treatment of the *BRCA* Mutation Carrier: Screening, Surveillance, and Management

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Chemotherapy for Patients with *BRCA1* and *BRCA2*-Mutated Ovarian Cancer: Same or Different?

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OVERVIEW

Retrospective studies have shown an improved prognosis, higher response rates to platinum-containing regimens, and longer treatment-free intervals between relapses in patients with *BRCA 1* and *BRCA 2* (*BRCA1/2*)–mutated ovarian cancer (BMOC) compared with patients who are not carriers of this mutation. These features of BMOC are attributed to homologous-recombination repair (HR) deficiency in the absence of *BRCA1/2* function, which results in an impaired ability of tumor cells to repair platinum-induced double-strand breaks (DSBs), thereby conferring increased chemosensitivity and increased sensitivity to poly(ADP-ribose) polymerase (PARP) enzyme inhibition and other DNA-damaging chemotherapeutic agents such as pegylated liposomal doxorubicin (PLD). Therefore, the chemotherapeutic approach for patients with BMOC should focus on treatment with platinum-based chemotherapy at first-line and recurrent-disease settings and measures to increase the platinum-free interval following early platinum-resistant relapse (i.e., progression-free survival of less than 6 months from last platinum-based chemotherapy) by using nonplatinum cytotoxic agents, with the aim of reintroducing platinum again at a later date. The role of first-line intraperitoneal platinum-based therapy in the specific context of BMOC also merits further analysis. Other than platinum, alternative DNA-damaging agents (including PLD and trabectedin) also may have a therapeutic role in patients with recurrent BMOC. The recent approval of olaparib for clinical use in Europe and the United States will also affect chemotherapeutic strategies for these patients. Further work to clarify the precise relationship between *BRCA1/2* mutation genotype and clinical phenotype is crucial to delineating the optimal therapeutic choices in the future for patients with BMOC.

The *BRCA1/2* tumor suppressor genes are critical for the maintenance of cellular genomic stability through the error-free repair of DNA double-strand breaks (DSBs) via the high-fidelity homologous-recombination repair (HR) pathway.[1,2] Loss of *BRCA1/2* function may occur because of somatic mutations or epigenetic silencing, which results in a dependency on alternative error-prone (low-fidelity) DNA repair pathways and potential genomic instability.[2] The absence of *BRCA1/2* function is associated with a cumulative lifetime risk for developing epithelial ovarian cancer (EOC) of 40% to 50% in patients who are *BRCA1*-mutation carriers and 20% to 25% in patients who are *BRCA2*-mutation carriers.[3] Germ-line mutations in *BRCA1/2* have been observed in 14% of patients with nonmucinous EOC, including 17% of patients with high-grade serous histology, with 44% of these patients having no reported family history of breast or ovarian cancer, whereas somatic mutations in *BRCA1/2* have been found in 6% of patients with high-grade serous EOCs.[4,5]

PLATINUM SENSITIVITY AND IMPROVED SURVIVAL ARE HALLMARKS OF BRCA-NESS IN EOC

Improved prognosis in terms of progression-free survival (PFS) and overall survival (OS), with higher partial response (PR) and complete response (CR) rates to platinum-containing regimens and longer treatment-free intervals, has been observed in retrospective studies of patients who are *BRCA1/2*-mutant carriers with ovarian cancer compared with patients who are non-BMOC.[5-10] This "BRCAness" phenotype, with superior outcomes following platinum-based therapy in patients with BMOC, has been attributed to HR deficiency in the absence of *BRCA1/2* function. This results in an impaired ability of *BRCA*-deficient tumor cells to repair platinum-induced DSBs, which confers increased sensitivity to chemotherapy.[8,9,11] Similarly, inhibition of poly(ADP-ribose) polymerase (PARP) enzymes (which repair single-stranded DNA breaks mainly through the base-excision repair pathway) in HR-deficient cells by PARP inhibitors (PARPi) results in DSBs that are subjected to low-fidelity repair by nonhomologous end joining.[2,12] The absence of high-fidelity DNA-repair mechanisms following PARPi treatment in HR-deficient cells leads to synthetic lethality through an accumulation of DNA damage that results in mitotic catastrophe and cell death.[13] PARP inhibitors are active agents in patients with BMOC, but they also may be effective in a subset of sporadic ovarian cancers.[14] Mutations

in other genes, such as *ATM, CHEK1, CHEK2, NBN,* and *RAD51D,* can also affect HR function and increase sensitivity to DNA-damaging agents and PARPi.[11]

WHAT ARE THE MECHANISMS OF PLATINUM RESISTANCE IN BMOC TUMORS?

Recent evidence suggests that secondary (reversion) *BRCA1/2* mutations are a mechanism of acquired resistance to platinum and PARPi in *BRCA1/2*-mutated cancer cells.[15,16] Reversion of *BRCA1/2* germ-line mutations also have been found in platinum-resistant tumors,[17] but it is unclear which functions of BRCA1/2 proteins are required for therapy resistance and which *BRCA1/2* genotypes are more likely to undergo reversion mutations. Furthermore, it is unclear if a spectrum of platinum and PARPi sensitivity exists among *BRCA1/2* mutant cancers, such that, independent of reversion mutations, certain *BRCA1/2* genotypes may be associated with a phenotype that is intrinsically less sensitive to these therapies than others or may be associated with heterogeneity in their response to these therapies, such that the tumors are platinum resistant but still retain sensitivity to PARPi and vice versa. Heterogeneity in clinical response also may be explained by other mechanisms of (PARPi) resistance, including enhanced P-glycoprotein-mediated drug efflux or reduced 53BP1 expression.[18]

Evidence to support the notion that all *BRCA1/2*-mutated cancers may not have a uniform clinical phenotype has emerged from survival data showing that patients with EOC who carry a germ-line *BRCA2*-mutation have a better prognosis than patients with EOC who carry a germ-line *BRCA1*-mutation.[6] Furthermore, recent in vivo data from a *BRCA1*-deficient mouse mammary carcinoma model suggest that the *BRCA1C61G* mutation (a common pathogenic missense variant) may be associated with poor response and rapid development of resistance to platinum drugs and PARP inhibition but still retain the *BRCA1C61G* mutation.[19] This suggests that ab initio resistance to specific chemotherapeutic agents may also exist in certain *BRCA1/2*-mutated breast and ovarian cancers depending on the patient's *BRCA1/2* genotype. In a recent meta-analysis of clinical outcome data in patients with BMOC, *BRCA1/2* mutations and low *BRCA1* expression by immunohistochemistry or reverse transcription polymerase chain reaction were statistically significantly better prognostic factors for survival (hazard ratio [HR] 0.51 to 0.67), whereas *BRCA1*- promoter methylation was not associated with improved prognosis (HR 1.59).[10] Therefore, given the potential effect of the mechanisms of *BRCA1/2* inactivation and genotype on the heterogeneity of treatment responses and outcome, the ability to correlate *BRCA* genotype with its clinical "BRCAness" phenotype will be crucial to facilitate patient stratification according to underlying *BRCA1/2* deficiency in each patient to optimize management in the future.

WHAT DATA EXIST FOR INCREASED SENSITIVITY TO SINGLE AGENT CHEMOTHERAPEUTIC DRUGS OTHER THAN PLATINUM COMPOUNDS IN PATIENTS WITH BMOC?

Limited data are available presently to fully address the question of whether chemosensitivity to platinum salts observed in patients with BMOC can be extended to other nonplatinum agents, including pegylated liposomal doxorubicin (PLD), paclitaxel, topotecan, and gemcitabine, which commonly are used as monotherapy in the platinum-resistant/refractory setting (Table 1).

The most convincing information comes from two retrospective analyses on patient outcomes following treatment with PLD in BMOC. Both have demonstrated improved response rates and PFS when compared with patients who are non-BMOC.[22,28] Safra et al combined the outcomes of patients who received either PLD as a single agent or in combination with platinum-based chemotherapy and demonstrated improved median time to treatment failure (15.8 vs. 8.1 months; p = 0.009) and OS (56.8 vs. 22.6 months; p = 0.002) for patients with BMOC vs. patients who are non-BMOC.[28] Adams et al examined the response rates of 23 patients with BMOC following treatment with single-agent PLD and reported an improved response rate of 56.5% (3 by RECIST criteria and 10 by CA125 levels) in patients with BMOC compared with only 19.5% (2 by RECIST criteria and 6 by CA125 levels; p = 0.004) in patients who are non-BMOC.[22] Notably, 71% (10/14) of BMOC patients with platinum-resistant disease in this study responded to PLD,

KEY POINTS

- Improved prognosis and response to platinum-based chemotherapy are hallmarks of *BRCA1/2*-mutated ovarian cancer (BMOC).
- Increased platinum sensitivity is attributed to underlying homologous-recombination repair deficiency in BMOC, leading to impaired ability to repair platinum-induced double-strand breaks, thereby conferring increased sensitivity to chemotherapy.
- Chemotherapeutic strategies for patients with BMOC should focus on platinum-based chemotherapy at first-line and recurrent-disease settings, and include measures to increase the platinum-free interval in patients with early platinum-resistant relapse (i.e., progression-free survival of < 6 months from last platinum-based chemotherapy) by using nonplatinum cytotoxic agents, with the aim of reintroducing platinum at a later date.
- In recurrent disease, patients with BMOC appear to have increased sensitivity to pegylated liposomal doxorubicin and other DNA-damaging agents, including trabectedin and mitomycin C, also may have a therapeutic role.
- With recent approval for the use of the poly(ADP-ribose) polymerase (PARP) inhibitor (PARPi) olaparib in BMOC in Europe and the United States, further work to define the optimal choice, timing, and sequence of chemotherapy and/or PARPi therapy will be crucial to improve outcomes for patients with BMOC.

TABLE 1. Overall Response Rates following Chemotherapy in Patients with BMOC

Chemotherapy Regimen	ORR in Platinum-Sensitive BMOC	ORR in Platinum-Resistant BMOC	References
Platinum-Based Chemotherapy	**First Line**		
	87%[a] *BRCA1* (83 patients)	-	Vencken et al[9]
	92%[a] *BRCA2* (13 patients)	-	Vencken et al[9]
	96%[b] (21/22 patients)	-	Tan et al[8]
	Recurrent		
	65%[c] (48 patients)	80%[c] (8/10 patients)	Alsop et al[5]
	92%[b] (11/12 patients, second line)	-	Tan et al[8]
	100%[b] (7/7 patients, third line)	-	Tan et al[8]
	100%[d] (6/6 patients)	-	Leunen et al[20]
Paclitaxel Monotherapy	60%[b] (9/15 patients)	27%[b] (3/11 patients)	Tan et al[21]
Pegylated Liposomal Doxorubicin	57%[d] (13/23 patients)	77%[d] (10/14 patients)	Adams et al[22]
	39%[d] (13/33 patients) in relapsing disease < 12 months after most recent platinum-based chemotherapy	-	Kaye et al[23]
Trabectedin	41%[b] (36/88 patients)	-	Lorusso et al[24]
Topotecan	-	0% (0/9 patients)	Hyman et al[25]
Mitomycin C	33%[e] (2/6 patients)	66%[e] (4/6 patients)	Moiseyenko et al[26]
Melphalan	-	CR in 1 patient	Osher et al[27]

Abbreviations: ORR, overall response rate; BMOC, *BRCA1*- and *BRCA2*-mutated ovarian cancer.
[a] World Health Organization criteria were used to evaluate response to chemotherapy.
[b] Response Evaluation Criteria in Solid Tumors (RECIST) criteria.
[c] Response defined as a 50% decrease in CA-125, maintained for 28 days.
[d] RECIST PR/CR and Gynecologic Cancer Intergroup (GCIG) CA-125 criteria.
[e] RECIST PR/CR or more than 50% reduction in CA-125.

and improved PFS and OS measured from the time of PLD administration also was observed.[22] Furthermore, the improved outcomes noted in both studies appeared to be independent of platinum sensitivity.[22,28] An improved response to PLD also was a striking feature in a randomized study of patients with BMOC with relapsed disease within 12 months of completing platinum-based therapy.[23] Patients were randomly assigned to (two dose levels of) olaparib or PLD; at 400 mg twice a day olaparib yielded the expected 59% RECIST/CA125 response rate with a median PFS of 8.8 months. PLD yielded an unexpectedly high level of 39% combined RECIST/CA125 response with a median PFS of 7.1 months.[23]

Given that doxorubicin is a topoisomerase II-alpha poison that causes DSBs in DNA by inhibiting the unwinding of DNA for transcription and replication,[29] the increased efficacy of PLD in patients with BMOC also could be directly related to defective HR in BMOC cells. Intriguingly, however, in a small study by Hyman et al, no responses were observed following treatment with the topoisomerase I inhibitor topotecan in nine patients with BMOC who received heavy pretreatment.[25] Likewise, Safra et al demonstrated no difference in PFS (median PFS of 4 months in both groups) between patients with BMOC or who are non-BMOC who were treated with topotecan.[30] It is unclear why the differences in outcomes observed for topoisomerase I and II inhibition exist. Possible explanations include the additional cytotoxic effects of doxorubicin beyond topoisomerase II inhibition (e.g., intercalation into DNA causing additional DSBs, inhibition of DNA synthesis, and generation of free radicals, coupled with the fact that PLD may have

improved drug delivery properties that could potentially enhance its antitumor effect).[31,32] Furthermore, a recent study demonstrated that although the cytotoxic response to PLD was similar in *BRCA1*-deficient and wild-type cells in vitro, *BRCA1* inactivation resulted in higher expression of Fas and MHC-I both before and after PLD exposure.[33] Additionally, PLD prolonged the survival of *BRCA1*-deficient tumor-bearing mice and increased intratumoral T-cell recruitment. Subsequent depletion of CD4$^+$ T cells combined with PLD treatment also substantially prolonged overall survival in *BRCA1*-deficient tumor-bearing mice.[33] Therefore, the increased efficacy of PLD also may be related to the amplification of its immunomodulatory effects in BMOC tumors, which may, in turn, enhance host antitumor responses.

Trabectedin, a minor groove DNA-binding agent derived from the marine organism Ecteinascidia turbinate, is approved in some countries for treating relapsed ovarian cancer in combination with PLD. Preclinical data suggest enhanced activity in HRD cells. Furthermore, at the 2014 American Society of Clinical Oncology Annual Meeting, Lorusso et al reported data on 88 patients with EOC with documented *BRCA1/2* mutation or BRCAness phenotype (defined as at least two previous responses to platinum) treated with single-agent trabectedin. An overall response rate of 41% was noted, with a median PFS of 18 weeks and a median OS not reached.[24] However, the significance of this is uncertain because the patient group was described as moderately or highly platinum-sensitive, and in previous phase II studies of single-agent trabectedin in unselected patients, the response

rate in platinum-sensitive patients was reported as 29% to 36%.[34,35] A second piece of clinical data has suggested a correlation between *BRCA1/2*-mutation status and the improved efficacy of trabectedin/PLD over PLD alone in a subgroup analysis of 41 patients in the OVA-301 trial. This observation may merit further exploration of that combination.[36]

Clinical data on smaller numbers of patients were reported in support of preclinical results suggesting increased sensitivity to other DNA-damaging agents such as mitomycin-C[37] and melphalan[38] for *BRCA1/2*-deficiency. Moiseyenko et al recently reported that administration of mitomycin-C (10 mg/m², 4 doses per week), which induces DNA cross-links, resulted in one CR (duration 36 weeks), two PRs (duration 36 and 48 weeks) and six instances of disease stabilization of between 12 to 24 weeks duration in patients with BMOC with recurrent disease.[26] Melphalan is a bifunctional alkylating agent that induces inter- and intrastrand DNA cross-links. It has been shown to be selectively toxic to *BRCA2*-deficient breast cancer cell lines.[38] Single doses of melphalan also have resulted in longer relapse-free survival in mice xenografted with *BRCA2*-deficient cells than with cisplatin or olaparib in vivo.[38] Osher et al reported a case of a patient who was a *BRCA2* mutation carrier with platinum-resistant EOC who responded to treatment with oral melphalan (8 mg per day, 5 days per month for 1 year) and has remained disease-free for more than 25 years.[27]

Paclitaxel is a well-established therapeutic agent for treating patients with EOC in the first-line[39] and relapsed settings.[40] In the context of patients with BMOC, however, the sensitivity of *BRCA1*-mutated cancer cells to platinum chemotherapy has been reported to correlate inversely with sensitivity to microtubule-interfering agents such as taxanes.[41] Furthermore, inhibition of *BRCA1*-expression in ovarian cancer cell lines has shown to increase cellular sensitivity to platinum compounds but reduce antitumor activity of taxanes.[42,43] Clinical data were also provided to suggest that overall survival for patients with higher *BRCA1*-expressing ovarian cancers improved following taxane-containing chemotherapy, albeit nonsignificantly (23.0 vs. 18.2 months; p = 0.12; HR, 0.53),[42] thus suggesting that higher *BRCA1*-expression levels may be required for a clinical response to taxanes. In vitro data suggest that *BRCA1*-mutated breast cancer cells are resistant to paclitaxel, in contrast to *BRCA1* wild-type cells,[44] and MCF-7 cells transfected with *BRCA1* siRNA display a significant 9-fold increase in resistance to paclitaxel (p ≤ 0.001).[45] Taken together, these data imply that patients with BMOC who harbor defects in *BRCA1/2* function through germ-line or sporadic mutations also may be potentially resistant to paclitaxel.[43] However, conflicting preclinical published studies indicate reduced *BRCA1* expression actually may confer increased sensitivity to paclitaxel.[46,47] In this context, a study by Tan et al of 26 patients with BMOC who received paclitaxel monotherapy for relapsed disease described an overall response rate of 46% (12 of 26 patients).[21] The clinical benefit rate (defined as RECIST PR or CR, or stable disease after 18 weeks of treatment) was significantly higher (80 vs. 36%, p = 0.04) in patients who are platinum sen-

sitive than in patients who are platinum resistant.[21] These data do not suggest any adverse effect of *BRCA1/2* mutation carrier status on the activity of paclitaxel. The study also showed that patients with BMOC who were platinum sensitive had significantly longer median PFS compared with patients who were platinum resistant (42 vs. 21 weeks, p = 0.003).[21] In the retrospective study by Safra et al, PFS for patients with BMOC following paclitaxel monotherapy was not significantly different from that of patients who are non-BMOC (p = 0.572).[30] Overall, the data suggest that equivalent paclitaxel efficacy is seen in both groups of patients, and taxanes should continue to have a therapeutic role in patients with EOC regardless of *BRCA1/2* carrier status.

ARE THERE ANY CHEMOTHERAPY COMBINATION DATA IN THIS CONTEXT?

In a retrospective single-institute review of 256 patients, the combination of PLD and platinum or gemcitabine and platinum was associated with significantly improved PFS in patients with BMOC compared with patients who are non-BMOC (p = 0.001 and p = 0.02, respectively); however, there were no differences in outcome when taxanes were used in combination with platinum.[30] As such, it is tempting to speculate that a PLD/platinum combination potentially may be a better option than a taxane/platinum combination at some stage of treatment for patients with BMOC. However, no prospective comparative data presently support this. The two randomized trials that compared their efficacy in the first-line (MITO-2 trial)[48] and recurrent (CALYPSO trial)[49] settings did not include subgroup analyses of patients with BMOC vs. patients who are non-BMOC. There is a good case, however, to retrieve samples in these trials for *BRCA1/2*-mutation testing.

HOW SHOULD PATIENTS WITH BMOC BE TREATED AT PRESENT?
First-Line Chemotherapy for Patients with BMOC

In recurrent disease, the retrospective data appear to suggest that PLD may be superior to paclitaxel as a single agent, but the situation for carboplatin-based combinations in first-line treatment may be quite different. Although some may consider the option of PLD/carboplatin as the first-line treatment of choice in newly diagnosed patients with BMOC, there are no randomized data to support this approach. Data from the JGOG3016 study demonstrating significantly superior PFS and OS outcomes when carboplatin is combined with dose-dense weekly paclitaxel instead of thrice weekly paclitaxel also should be taken into account (PFS, p = 0.0037; OS, p = 0.039).[50] Therefore, although the PLD/carboplatin combination represents a viable alternative to the current standard of paclitaxel/carboplatin in patients with BMOC who wish to reduce the risk of neuropathy, which is in line with the data from MITO-2,[48] there are currently no data to support dropping paclitaxel routinely from first-line chemotherapy for patients with BMOC.

The role of first-line intraperitoneal (IP) chemotherapy for patients with EOC remains controversial despite the positive data from the GOG-172 phase III randomized trial of intravenous paclitaxel and cisplatin compared with intravenous paclitaxel and IP cisplatin plus IP paclitaxel in patients with optimally resected stage III EOC.[51] However, a recent retrospective analysis of tumor samples taken from patients in the trial revealed a 36-month survival improvement in patients treated with IP chemotherapy who had decreased *BRCA1* expression (defined as ≤ 10% immunohistochemical staining) in their archival tumor compared to intravenous treatment.[52] Further analyses of the *BRCA1/2* mutation status of tumor samples from other ongoing IP trials, including GOG 252, OV-21/GCIG, and the iPocc study,[51] may help consolidate the data regarding its role in patients with BMOC.

Chemotherapy for Patients With Recurrent BMOC

For patients with recurrent EOC, the choice of chemotherapy should probably take *BRCA1/2* mutation status into account. First, as to platinum-resistant recurrent disease, it is unclear if the current clinical definition of platinum sensitivity and resistance in recurrent EOC, based on the 6-month platinum-free interval, accurately predicts the likelihood of response when patients with BMOC are rechallenged with platinum-based chemotherapy. In a small subgroup of the Australian series, Alsop et al reported that 80% (8 of 10) of patients with BMOC with recurrent disease who experienced relapse within 6 months of their last platinum chemotherapy treatment subsequently responded when rechallenged with platinum-based chemotherapy.[5] This provides a tantalizing signal that patients with BMOC may have increased ability to regain platinum sensitivity even after platinum resistance develops and we should perhaps be less conservative with the definition of platinum resistance in the context of BMOC. To some extent, this feature of BRCAness also may explain why responses to platinum-based chemotherapy can still be attained in a proportion of patients with EOC in the platinum-resistant/refractory setting.[53,54] Based on the data in the small subgroup described by Alsop, and leaving the role of PARPi aside for the moment, a possible option would be early rechallenge with platinum-based chemotherapy for patients with BMOC who are platinum-resistant. However, a more logical option, if available, probably would be to extend the platinum-free interval by first using a nonplatinum-based agent in the platinum-resistant setting before reintroducing platinum at disease progression. Options for prolonging the platinum-free interval include incorporating a course of single agent PLD (and it would be interesting to elucidate the benefit of PLD rechallenge for patients who previously were treated with PLD in combination with platinum)[23] or weekly paclitaxel with or without bevacizumab based on data from the AURELIA trial.[55] At any rate, serious consideration always should be given to patients with BMOC and platinum-resistant disease who have a 12-month or more platinum-free interval (perhaps through intervening PLD or weekly

taxol) to be retreated with carboplatin-based chemotherapy (or cisplatin, if needed because of hypersensitivity). Using this paradigm, patients with BMOC may benefit from multiple lines of platinum-based therapy. At the Royal Marsden, for example, a 55-year-old patient received 8 courses of platinum-based treatment over 10 years.

For platinum-sensitive recurrences, the choice of chemotherapy for patients with BMOC probably mirrors that of any patient with platinum-sensitive recurrent EOC. Nonetheless, the PLD/platinum or gemcitabine/platinum combination may be the preferred choices in view of the aforementioned data. Finally, Leunen et al reported a response rate of 100% and a median OS of 37 months in a small series of six patients with BMOC with recurrent platinum-sensitive EOC who were treated with dose-dense paclitaxel and carboplatin,[20] but more experience with the combination is necessary before any conclusions can be drawn.

WHAT EFFECT WILL THE RECENT REGULATORY APPROVAL OF PARP INHIBITORS HAVE ON THE CHOICE OF CHEMOTHERAPY FOR PATIENTS WITH BMOC WITH RELAPSED DISEASE?

The first PARPi, olaparib, is now approved for treating patients with BMOC by regulatory authorities in both the United States and Europe, but in two different clinical situations. In the United States, approval has been granted for patients with BMOC who have received at least three lines of prior chemotherapy (and may be platinum resistant). Given the level of efficacy seen, (response rate of 31% with median PFS of 7 months), it seems likely that olaparib will be increasingly used before any alternative chemotherapy in this situation.[56] Approval was not granted for maintenance treatment. Conversely in Europe, approval is granted only in the maintenance setting following the placebo-controlled trial in patients with platinum-sensitive relapse by Ledermann et al, in which patients in the BMOC subgroup had a 7-month prolongation in median PFS (HR < 0.0001).[57] Olaparib was given following, but not concurrently, with platinum-based chemotherapy.

This development leads to a major therapeutic dilemma for the clinician and the patient with platinum-sensitive relapsed BMOC, since two options are now available. The first would be the use of bevacizumab in line with the positive data in this context when used concurrently with gemcitabine/carboplatin, and as follow-on maintenance treatment, which demonstrated a PFS increase of 4 months (HR 0.48).[58] The second is the olaparib option described above. Both require carboplatin-based treatment. Presently, the bevacizumab option requires this to be gemcitabine-carboplatin, which has to be given at first platinum-sensitive relapse. For the olaparib maintenance therapy option, the carboplatin partner is not specified and the treatment could be used at any relapse, providing it fulfills the criteria for platinum sensitivity. It would, therefore, be tempting to suggest that bevacizumab should be used first; however, the next

relapse could conceivably be platinum-resistant. In Europe, but not in the United States, this would deprive the patient with BMOC of the opportunity to receive a PARPi. Thus, in Europe it might be tempting to recommend olaparib first because bevacizumab could be given later in the context of platinum resistance (where it is approved according to the AURELIA data[55]). However, if the next relapse in that situation was still platinum sensitive, bevacizumab could not be given. According to the current label, it only can be used for the first platinum-sensitive relapse. The dilemma in Europe is clear, and this common clinical scenario will require careful discussion with patients with BMOC when the choice of chemotherapy in the platinum-sensitive relapse situation occurs. One way forward is to consider carefully the platinum-free interval in these patients as a way of predicting whether the next relapse is likely to be platinum sensitive or platinum resistant. However, this is an inexact science. The situation will best be resolved when more data are available from further studies to permit a more uniform and flexible approach from the regulatory authorities in Europe and the United States.

WHAT EFFECT WILL THE USE OF A PARP INHIBITOR HAVE ON RESPONSE TO SUBSEQUENT CHEMOTHERAPY?

This is a particularly pertinent question in view of the previously discussed preclinical data suggesting that the development of PARPi resistance also may compromise benefit to subsequent chemotherapy, particularly platinum-based regimens, in patients with BMOC through the acquisition of reversion mutations in *BRCA1/2*.[15] A recently published study of chemotherapeutic response in patients with BMOC following progression on olaparib demonstrated a response rate of 36% (24 of 67 patients) by RECIST and 45% (35 of 78 patients) by RECIST and/or Gynaecologic Cancer Inter-Group (GCIG) CA125 criteria following postolaparib chemotherapy, with a median PFS and OS of 17 weeks and 34 weeks, respectively.[59] Response rates to platinum-based chemotherapy were 40% (19 of 48 patients) and 49% (26 of 53 patients), respectively, with a median PFS of 22 weeks and OS of 45 weeks. For patients who received single-agent paclitaxel, response rates were 40% (4 of 10 patients) by RECIST and 50% (5 of 10 patients) by RECIST and/or GCIG criteria. Patients who received postolaparib PLD had a 0% (0 of 5 patients) response by RECIST and 30% (3 of 10 patients) response by RECIST and/or GCIG criteria. Notably, no evidence of secondary *BRCA1/2* mutation was detected in tumor samples of six PARPi-resistant patients, suggesting that other yet to be determined mechanisms of resistance to PARPi may be involved. These data suggest that a proportion of BMOC tumors will retain chemosensitivity, particularly to platinum and paclitaxel despite progression on PARPi therapy. However, it is still not known completely how resistance to PARPi will affect the subsequent duration of chemotherapy response. To understand more fully the mechanistic interplay between PARPi and chemotherapy resistance, it will be important to systematically collect tumor samples and treatment outcome data to define the optimal chemotherapeutic options and relevant predictive biomarkers for patients with BMOC in the post-PARPi setting.

CONCLUSIONS: CHEMOTHERAPY FOR PATIENTS WITH *BRCA1/2* MUTATION AND OVARIAN CANCER: SAME, BUT DIFFERENT

The hallmarks of BMOC are a high response rate to platinum-based chemotherapy at first and subsequent relapses, long treatment-free intervals between relapses, and improved OS. These features describe the clinical signature of BRCAness in the context of EOC; however, so far they have been less well documented in other *BRCA1/2*-mutant carrier– related cancers including breast, pancreatic, and prostate cancer. This suggests that the context of the *BRCA1/2*-mutant genotype has a significant bearing on disease behavior and outcome. Nonetheless, very encouraging data on responses to PARPi in *BRCA1/2*-mutant carriers with prostate,[60] pancreatic,[56,61] and breast cancer[62] have been reported and are likely to be associated with platinum sensitivity.[63] It remains to be seen if an assay for HR-deficiency can be identified that will predict for platinum and PARPi sensitivity in a broad range of cancers. In the meantime, however, it is clear that establishing the germ-line and/or tumor *BRCA1/2* mutation status in patients with cancers known to be associated with *BRCA1/2* mutations is of paramount importance because of the potential therapeutic options.

Our recommendations for chemotherapy for patients with BMOC are generally based on retrospective analyses, with a primary emphasis on rechallenging these patients with platinum-based treatment and prolonging the platinum-free interval in the event of early relapse following platinum-based treatment. The welcome arrival of using PARPi to treat patients with BMOC also provides an additional initial factor to consider within the context of relapsed disease. Hence, although a majority of treatment options remain the same for both patients with BMOC and with non-BMOC, the timing and sequence of therapy, and the indications for rechallenging patients with platinum-based chemotherapy, and perhaps even routes or schedules of administration (IV vs. IP, weekly vs. thrice weekly) are likely to differ as more data emerges from post hoc analyses of the mutation status of *BRCA1/2* and other HR-related genes in tumor samples from previously completed studies. Moreover, stratification based on HR-deficiency phenotype/genotype may become the standard in upcoming prospective clinical trials involving patients with EOC and that will be highly informative in this respect. Further work to dissect the precise relationship between *BRCA1/2*-mutation genotype and clinical phenotype also will be crucial to delineate the best treatment options in the future for patients with BMOC.

Disclosures of Potential Conflicts of Interest

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HEAD AND NECK CANCER

Best of the Rest: Top Head and Neck Abstracts from 2014–2015 Oncology Meetings

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Research Progress in Head and Neck Squamous Cell Carcinoma: Best Abstracts of ICHNO 2015

Panagiota Economopoulou, MD, PhD, Jean Bourhis, MD, PhD, and Amanda Psyrri, MD, PhD

OVERVIEW

Head and neck squamous cell carcinoma (HNSCC) is a highly heterogeneous group of tumors that develop via one of the two primary carcinogenic pathways: chemical carcinogenesis through exposure to tobacco and alcohol or virally induced tumorigenesis. HPV-negative (HPV−) and HPV-positive (HPV+) HNSCCs represent distinct disease entities, and the latter is associated with a substantially improved outcome. Differences in molecular pathogenesis account for these different outcomes; their staging classification and therapeutic regimens also are currently being re-evaluated, and re-evaluation would be significantly facilitated by robust biomarkers for patient stratification. Through the past years, with the advent of the omics era, a better understanding of the biology of HNSCC has been accompanied by the exploration of a large and rapidly expanding number of targeted agents, which might be incorporated into standard management in the future. In the era of personalized medicine, and with a view to improve the outcomes and quality of life of patients, current research efforts also are focused on the identification of specific biomarkers for treatment selection. Treatment of HNSCC is expected to change in the next decade if molecular biology continues to evolve. Herein, we highlight research progress in HNSCC presented at the fifth International Conference on Innovative Approaches in Head and Neck Oncology (ICHNO).

Squamous cell carcinoma of the head and neck represents a heterogeneous group of tumors, which encompasses a variety of tumors originating in the lip/oral cavity, hypopharynx, oropharynx, nasopharynx, or larynx. Locally advanced HNSCC includes stage III or IV A,B carcinomas that invade proximate structures or spread to cervical lymph nodes, whereas recurrent/metastatic (R/M) HNSCC involves tumors that present with locoregional recurrence or distant metastases.[1] HNSCC historically has been associated with tobacco and alcohol use; however, in the past decade, infection with high-risk HPV and especially with HPV type 16 (HPV16) has been implicated in the pathogenesis of a growing subset of HNSCCs, mainly those arising from the oropharynx.[2,3] HPV-related oropharyngeal carcinoma has emerged as a distinct entity in terms of etiology, biology, and clinical behavior; importantly, it has a more favorable prognosis and might require less intensive therapy. Despite advances and innovations in multimodality treatment and a better understanding of head and neck carcinogenesis, survival rates of locally advanced HNSCC have not substantially improved, and the prognosis for R/M disease remains very dismal.[4] The ultimate goal in the treatment of patients with HNSCC is to enhance efficacy while minimizing treatment-related toxic effects.

Current research in HNSCC focuses on the establishment of novel treatment approaches, such as immunotherapy and molecular targeted therapy; the identification of biomarkers for prognostic classification and treatment selection; optimization of surgical techniques; management of treatment-related side effects; and implementation of screening methods. This year, several interesting studies presented at the fifth ICHNO shared important information, with potential implications in the management of HNSCC. The results of a randomized phase III study comparing afatinib with methotrexate as a second-line therapy in patients with R/M disease after platinum therapy showed a significant but modest benefit of 0.9 months (p = 0.03) in terms of progression-free survival (PFS; the primary endpoint of the study) in favor of afatinib arm.[5] An individual-patient meta-analysis of chemotherapy in nonmetastatic nasopharyngeal carcinoma (MAC-NPC) that included 4,806 patients suggests that incorporating induction chemotherapy or adjuvant chemotherapy to chemoradiotherapy may further improve the outcome in terms of tumor control probability and survival compared with chemoradiotherapy alone.[6] A randomized phase III study randomly assigned patients with HNSCC who were treated with curative surgery and whose tumors had high-risk pathologic features (positive margins or extracapsular extension) to receive either standard postoperative radiotherapy (SPORT) or postoperative accelerated radiotherapy (POPART); the results suggest that a reduction in the overall treatment time in this setting does not improve the

outcome in terms of locoregional control, PFS, and overall survival (OS).[7] One study demonstrated that genomic analysis in R/M HNSCC enables an assessment of the molecular profile in 38% of patients and might guide targeted treatment selection.[8] Preclinical data support the combination of HPV vaccines with anti-programmed cell death protein 1 (anti-PD-1)– blocking antibodies to enhance the response to immunotherapy.[9] Finally, a large cohort study indicated that the current TNM (turmor, node metastasis) staging system is not suitable for HPV-associated HNSCC.[10]

HPV-ASSOCIATED OROPHARYNGEAL CANCERS
Therapeutic HPV Vaccine Increases Sensitivity of Poorly Immunogenic Tumor to Anti-PD-1 Monotherapy

The immune system plays an important role in cancer development, because tumor cells have the ability to evade immunosurveillance through a variety of different mechanisms, including reduced expression of tumor antigens, secretion of immunosuppressive cytokines such as transforming growth factor (TGF) beta, recruitment of immunosuppressive cells such as regulatory T cells (Tregs), and overexpression of certain ligands, such as programmed cell death ligand 1 (PD-L1).[11] PD-L1 binds to the PD-1 receptor and activates the PD-1 checkpoint pathway, which blocks the immune response by downregulating T-cell effector functions.[12] Several lines of evidence underscore the crucial role of an intact immune system in controlling HPV infection and its associated lesions. First, most healthy individuals infected with HPV are capable of clearing the infection, and they do not develop clinical manifestations.[13,14] Only a minority of infected individuals is not capable of clearing the virus and subsequently develops HPV-associated lesions. Second, immune cell infiltrates frequently are found in HPV-associated regressing lesions, whereas these cell types are absent in persistent lesions.[15] Finally, immunocompromised individuals, such as HIV-infected people, have documented higher rates of HPV infection and associated lesions.[16] Because the immune system plays a pivotal role in controlling HPV infection, therapeutic vaccine strategies have been developed. Therapeutic vaccines are aimed to treat HPV-infected cells, and this can be accomplished by inducing a cellular T-cell immune response that can recognize and eliminate these HPV-infected cells.[17]

HPV16 E6 and E7 proteins are ideal targets for cancer immunotherapy. HPV16 E6 and E7 are foreign viral proteins and are more immunogenic than a self-protein overexpressed in cancer cells. Furthermore, they are continuously expressed by all virus-infected cells.[18] Thus, DNA vaccines, viral vector vaccines, bacterial vector vaccines, peptide vaccines, and cell-based vaccines are attractive targets for investigation. DNA vaccines are promising candidates for therapeutic HPV vaccination in HPV-associated oropharyngeal carcinoma (OSCC).[19] Strategies to increase the activity of vaccines include using alternative administration routes, eliminating the immunosuppressive tumor microenviroment, and combining the vaccine with chemotherapy. In patients with HPV-associated oropharyngeal cancers, a high frequency of Tregs that inhibit cellular immune response often are found in tumor biopsies.[20] In addition, Lyford-Pike et al[21] demonstrated that the PD-1/PD-L1 pathway is involved in immune resistance of HPV-associated HNSCC.[21] PD-1 antibodies that inhibit the interaction between PD-1 and PD-L1 currently are being evaluated in clinical trials in a variety of cancers, leading to renewed enthusiasm for immunotherapy as a treatment modality. Pembrolizumab and nivolumab have been approved recently for the treatment of metastatic malignant melanoma.[22,23] The clinical response to anti-PD-1 antibodies has correlated with PD-L1 expression and with the presence of tumor-infiltrating lymphocytes in several tumors, including HNSCC.[24] Furthermore, novel anti-PD-L1 antibodies also are being evaluated in clinical trials in HNSCC. In this setting, Pai et al[9] suggested that a possible strategy to enhance responses to immune checkpoint blockade might be attenuation of immune responses to the host tumor by combining the HPV vaccine with a PD-1 antibody.[9] This strategy may facilitate PD-1 blockade–induced T-cell function restoration. The authors created a mouse model, with subcutaneous inoculation of tumor cells, that was poorly immunogenic and resistant to anti-PD-1 antibody; subsequently, they evaluated the impact of an HPV vaccine on improvement or response rates to anti-PD-1 blockade. The mice then were treated with either anti-PD-1–blocking antibody, CRT/E7 (detox) DNA vaccine, or a com-

KEY POINTS

- In vivo preclinical data suggest that HPV vaccination could act as an immune-stimulating agent resulting in improvement of response rates of HPV-positive oropharyngeal cancers to anti-PD-1 checkpoint inhibitor.
- A better-designed staging system of HPV-positive carcinoma that also encompasses prognostic factors such as age and tobacco use could alter treatment of these patients.
- A reduction in the overall treatment time of postoperative radiotherapy in patients with head and neck squamous cell carcinoma (HNSCC) with adverse factors for locoregional failure does not improve outcomes in terms of locoregional control, progression-free survival, and overall survival.
- LUX-Head and Neck 1 clinical trials comparing the efficacy of afatinib as monotherapy compared to single-agent methotrexate as second-line treatment in HNSCC met its primary endpoint showing an increase in progression-free survival of 0.9 months with afatinib compared to methotrexate, but in practical terms this modest effect is of unknown clinical importance.
- An individual patient data network meta-analysis of the treatment of nonmetastatic nasopharyngeal carcinoma suggests that incorporating induction chemotherapy or adjuvant chemotherapy to chemoradiotherapy may further improve the outcome in terms of tumor control probability and survival over chemoradiotherapy alone.

bination of anti-PD-1 and CRT/E7 (detox) DNA vaccine. It was found that the administration of an HPV vaccine led to augmentation of vaccine-induced CD8^{+} T cells that express the PD-1 receptor. Concomitant upregulation of PD-L1 expression caused by the vaccine rendered tumor cells resistant to vaccine-induced cytotoxic T-cell killing, which was restored with anti-PD-1 treatment. Importantly, mice treated with combination of the two agents displayed better overall survival.[9] These in vivo preclinical data clearly suggest that HPV vaccination could act as an immune-stimulating agent, resulting in the improvement of response rates to an anti-PD-1 checkpoint inhibitor; this strategy deserves further study in a clinical trial setting.

Refining the UICC TNM Staging System Stage and Prognostic Groups for Nonmetastatic HPV-Related OSCC

As previously mentioned, OSCC includes two distinct entities: tobacco-alcohol associated OSCC, which is described as HPV– and HPV+ OSCC caused by persistent HPV infection. HPV+ OSCC is characterized by different clinical behavior; it commonly presents at an early T stage with extensive nodal involvement. On the basis of clinical presentation, distant metastasis could be a concern in HPV+ OSCC, as nodal infiltration at diagnosis is known to reduce 5-year survival by 50%. Nevertheless, HPV-related OSCC is associated with a better prognosis and might require different treatment.[2,25,26] Despite differences in clinical behavior between the two entities, the TNM staging system classification proposed by the American Joint Committee on Cancer (AJCC) is the most commonly used staging system in both HPV+ and HPV– HNSCC. Based on these observations, O'Sullivan et al[10] designed a large cohort study in an attempt to refine stage grouping for nonmetastatic OSCC and to develop several prognostic subgroups reflecting the different biology of the tumor that could be incorporated in the staging system.[10] In total, 537 patients with HPV+ OSCC and 237 patients with HPV– OSCC were included in the study. OS was compared among TNM stages for HPV+ and HPV– cases separately. Two different modeling methods were explored to derive a better stage schema for HPV+ disease: recursive partitioning analysis (RPA) derived new RPA stages objectively, and Cox regression was used to calculate an adjusted hazard ratio (AHR) to derive AHR stages. With a median follow-up time of 5.1 years, a lower 5-year OS with a higher TNM stage was observed in HPV– but not in HPV+ cases. In addition, RPA group, age, and smoking pack-years history derived four valid groups for survival: group I (T1 to T3N0 to N2c and 20 or fewer pack-years history), group IIa (T1 to T3N0 to N2c and more than 20 pack-years history), group IIb (T4 or N3, age 70 or younger), and group III (T4 or N3, older than age 70). The 5-year OS rates for the respective groups were 89%, 64%, 57%, and 40% (p < 0.001, Cox regression).[10] These results have potential implications in clinical practice, because a better-designed staging system of HPV+ disease that also encompasses prognostic factors, such as age and tobacco use, could alter management of the

HPV+ OSCC. However, these findings should be validated in large cohorts.

LOCALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA
POPART versus Conventional Postoperative Radiotherapy (CPORT) in HNSCC

Final results of a multicenter prospective randomized study of the Dutch Head and Neck Cooperative Study Group results are reviewed.

In HNSCC, the overall treatment time (OTT) of radiation is significantly associated with locoregional control (LRC; p = 0.013), which is consistent with rapid repopulation of cancer clones during radiotherapy (RT).[27] However, the importance of the OTT in the postoperative setting is not well defined. Langendijk et al[7] conducted a phase III study to determine the value of reduction of the OTT of postoperative RT in high-risk patients primarily treated with curative surgery.[7] Patients with HNSCC treated with curative surgery who had high-risk factors for locoregional recurrence (i.e., positive surgical margins and/or extracapsular extension) were randomly assigned to receive either SPORT at 2 Gy/fraction/day on 5 days/week to 66 Gy/33 fractions/7 weeks or POPART with 2 Gy/fraction/day on 5 days/week to 20 Gy followed by 1.8 Gy/fraction/day and 1.3 Gy/fraction/day to a boost field as a second daily treatment to 66.5 Gy/40 fractions/5 weeks.[7] The primary endpoint was LRC. Secondary endpoints were OS, PFS, acute and late toxicity, and quality of life. From November 2004 to August 2009, 148 patients were enrolled in the study (SPORT, 74 patients; POPART, 74 patients). The median follow-up time was 6.2 years. The two study arms were well balanced with regard to the most important prognostic factors. No significant differences were noted with regard to acute and late toxicity, although there was a trend toward more use of pain medication among patients treated with POPART. At 3 years, the LRC rate was 76.5% (95% CI, 67.0% to 87.4%) after POPART compared with 74.2% (95% CI, 64.6% to 85.0%) with SPORT (hazard ratio [HR] 0.75; 95% CI, 0.40 to 1.43; p = 0.39). No difference was found with regard to PFS (HR 0.74; 95% CI, 0.49 to 1.13; p = 0.16). The median PFS times were 42.6 months (95% CI, 31 to 78.3 months) for SPORT and 60.5 months (95% CI, 34.6 months to not achieved [NA]) for POPART. The disease-free survival probability at 8 years was 43.8% for SPORT (95% CI, 33.8% to 57.0%) and 51% for POPART (95% CI, 40.7% to 63.8%). No statistical difference was noted in the long term between the two arms. The 8-year overall survival rate was 46.0% for POPART compared with 33.1% for SPORT (HR 0.82; 95% CI, 0.53 to 1.28; p = 0.39).[7] These results suggest that a reduction in the OTT of postoperative RT in patients with HNSCC who have adverse factors for locoregional failure does not improve outcome in terms of LRC, PFS, and OS.

RECURRENT/METASTATIC HEAD AND NECK SQUAMOUS CELL CARCINOMA

Afatinib versus Methotrexate as Second-Line Therapy in Recurrent/Metastatic HNSCC after Platinum Therapy: LUX Head and Neck 1

For patients with R/M HNSCC, the recommended first-line treatment is combination platinum/fluorouracil with or without cetuximab for fit patients.[1] Limited options are available for second-line therapy, and, unfortunately, a small proportion of patients are fit enough to be suitable candidates for second-line therapy. The epidermal growth factor receptor (EGFR), a transmembrane tyrosine kinase receptor belonging to the HER/ErbB family, is a longstanding, challenging target in HNSCC, which is overexpressed in up to 90% of cases; overexpression of EGFR also correlates with poor clinical outcomes.[28,29] Cetuximab, a chimeric immunoglobulin G1 human monoclonal antibody against the extracellular domain of EGFR, has emerged as a powerful tool in the treatment of R/M head and neck cancer, and it is the only targeted agent currently approved for HNSCC. In the EXTREME (erbitux in first-line treatment of recurrent or metastatic head and neck cancer) study, the addition of cetixumab to platinum-based chemotherapy with fluorouracil was shown to improve OS, PFS, and response rates.[30] However, cetuximab has demonstrated modest response rates when used as monotherapy.[31] Afatinib, an oral irreversible ErbB family blocker that inhibits all kinase-active members (EGFR, HER2, and HER4), and which is currently approved for the treatment of *EGFR*-mutated non–small cell lung cancer,[32] has shown similar clinical activity to cetuximab in R/M HNSCC in a recent phase II trial.[33] On the basis of these results, the phase III LUX Head and Neck 1 clinical trial presented at the 2014 European Society of Medical Oncology Congress assessed the efficacy of afatinib as monotherapy compared with single-agent methotrexate as second-line treatment in HNSCC.[5] Patients were stratified according to performance status (PS) and prior use of cetuximab. The study met its primary endpoint, showing an increase in PFS of 0.9 months with afatinib compared with methotrexate (2.6 vs. 1.7 months; HR, 0.8; p = 0.03). In addition, it showed improvement in tumor shrinkage and response rate in favor of afatinib, whereas no improvement in OS with afatinib versus methotrexate was noted. Grades 3 and 4 treatment-related adverse events were skin rash (9.7%) and diarrhea (9.4%) with afatinib and stomatitis (8.1%) and neutropenia (6.9%) with methotrexate. A significant delay in the deterioration of global health status, pain, and swallowing was noted with afatinib. In practical terms, the difference in PFS of 0.9 months is of unclear significance and is unlikely to lead to drug approval.[5] However, this study is important, because it is the second study since the EXTREME trial that showed a benefit of a novel agent in HNSCC and the first study to demonstrate an active oral, targeted agent in HNSCC. Of note, subgroup analysis showed a benefit primarily seen in cetuximab-naive patients, which suggested a degree of cross-resistance that was not seen in phase II studies. Ongoing studies evaluating adjuvant afatinib in locally advanced HNSCC after chemoradiotherapy (LUX Head and Neck 2) hopefully will clarify the role of afatinib in HNSCC; until then, an active search for predictive biomarkers might lead to the identification of specific groups of patients who derive benefit from afatinib.

Molecular Screening for Cancer Treatment Optimization in Head and Neck Cancer: MOSCATO 01

In the era of personalized medicine, there is a push toward utilizing next-generation sequencing to identify driver mutations in individual tumors. The identification of driver molecular alterations in individual tumors may allow personalization of cancer therapy. Targeted agents matched with tumor molecular alterations were associated with improved outcomes compared with nonmatched therapy in patients who had advanced cancers, in some studies.[34] Recently, four whole-exome sequencing studies conducted in 190 HNSCC specimens shed light onto the molecular pathogenesis of HNSCC, identifying key mutations of several tumor suppression genes, such as *TP53* (60%), *CDKN2A* (9% to 74%), *PI3KCA* (8% to 20%), *Notch* (9% to 19%) and *PTEN* (13.6%).[35-38] These studies revealed, for the first time, the presence of novel inactivating mutations in tumor suppressor genes that regulate cellular squamous differentiation within the normal stratified squamous epithelium, such as *NOTCH1*, *TP63*, and *FBXW7*, as driver genetic events of neoplastic transformation in the head and neck area. Elucidation of the mutational spectrum of HNSCC is anticipated to have a great impact on the treatment of the various subtypes of the disease according to the constellation of targetable driver genetic events. In a prospective study that included 78 heavily pretreated patients with HNSCC, biopsy specimens obtained from the primary or metastatic tumor sites were subjected to comparative genomic hybridization and next-generation sequencing for up to 74 target genes (10% tumor cells required).[8] A weekly molecular tumor board reviewed the results of the molecular analysis to identify actionable molecular alterations for which the most relevant targeted therapy may be available through early clinical trials or approved drugs. In 30 of 78 heavily pretreated patients included in the MOSCATO 01 trial, actionable molecular aberrations were encountered and were defined as aberrations with significant prognostic and therapeutic implications for specific drugs currently used in other cancers. One-third of those patients were treated with a targeted therapy according to the molecular profile. Among patients treated on the basis of the genomic profile, three attained partial response, three had stable disease, one developed disease progression, and two were not evaluable. In this study, actionable molecular aberrations were observed in the following pathways: fibroblast growth factors (FGFs) and their receptors (FGFRs; 35%), phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) (26%), *MYC* (24%), CDKs/Cyclins (13%), *EGFR* (9%), *HER2* (7%), *Notch* (4%), and *KIT* (2%).[8] This study shows early results of a personalized medicine strategy in R/M HNSCC, and further results will be awaited with great interest. It is important to emphasize, however, that implementing a personalized cancer medicine program requires adequate tumor tissue available for molecular characterization; a standardized, high-quality laboratory for molecular profiling to ensure the accuracy, reliability, and timeliness of

patient test results; identification of targetable molecular aberration; and the availability of a targeted drug known to inhibit the function of the molecular alteration.[39] High-throughput sequencing technology provides the means to conduct a comprehensive analysis of all somatic alterations in the cancer genomes. However, interpretation of the large amount of genomic data that emerge from these genome-scale investigations for the development of new therapeutic strategies requires the efficient validation of genomic data and the characterization of mutations. It is important to determine whether the identified mutations are responsible for disease pathogenesis (driver mutations) or have been generated as the consequence of genomic instability but without obvious advantage to the cancerous cells (benign mutations). To address the challenge of fragmentation of cancer research in Europe that generates difficulties in translating preclinical discoveries into benefits that improve patients' lives, the Eurocan Plus project aims for the establishment of a European platform for translational cancer research by linking comprehensive cancer centers and basic/preclinical research centers.[39] The Eurocan Platform project was approved by the European Commission in 2010 and aims to develop a consortium for translational cancer research by linking 23 cancer research centers and five European cancer organizations. One of the most important aims is to promote personalized cancer medicine that is based on the better understanding of the biology of the tumor and normal tissues so that personalized treatment can be applied at an early stage of the disease. Furthermore, prevention strategies should be established in cancer biology to identify and target high-risk individuals.

NASOPHARYNGEAL CANCER
What Is the Best Treatment in Nasopharyngeal Carcinoma? An Individual Patient Data Network Meta-Analysis

With the improvement in local control accomplished by more precise imaging and RT, the predominant pattern of failure for nasopharyngeal carcinoma (NPC) is distant metastases. Concurrent cisplatin and RT with or without adjuvant PF (cisplatin/

fluorouracil) chemotherapy is the standard treatment approach for stages IIB and above disease.[1] The role of induction chemotherapy is not well defined. MAC-NPC presented the results of network meta-analysis, which allows one to perform simultaneous inference regarding the treatments and select the best among them.[6] Nineteen trials of RT with or without chemotherapy in 4,806 patients with nonmetastatic NPC were identified, and updated individual patient data were obtained. Treatments were grouped in the following categories: RT alone (RT), induction chemotherapy (IC) followed by concomitant chemoradiotherapy (IC-CRT), concomitant chemoradiotherapy (CRT), or concomitant chemoradiotherapy followed by adjuvant chemotherapy (CRT-AC). For the entire network, CRT-AC ranked as the best treatment in terms of OS, with a probability of 94%.[6] The probability that either CRT-AC or IC-CRT was the best treatment was 97% for OS, 96% for PFS, 81% for locoregional failure-free survival, and 93% for distant metastasis-free survival. When the network was restricted to cisplatin-based trials, as a sensitivity analysis, CRT-AC and IC-CRT remained the best treatments regarding PFS and OS.[6] This network meta-analysis of the treatment of nonmetastatic NPC suggests that incorporating IC or AC to CRT may further improve the outcome in terms of tumor control probability and survival versus CRT alone. Of course, as the authors point out, these results should be validated by well-powered randomized trials.

CONCLUSION
HNSCC comprises a heterogeneous disease in terms of epidemiology, etiologic factors, and clinical and biologic behavior. HPV status is the most important biomarker in this disease. Research efforts concentrate on identification of prognostic and predictive biomarkers for the personalization of treatment, deintensification of treatment to reduce late toxicity in good-prognosis HPV+ subsets, and the discovery of new treatments in poor-prognosis HPV− HNSCC. Immunotherapy, such as checkpoint inhibitors, is being explored as treatment strategy in HNSCC in different settings. In Europe and the United States, research funding for new treatments in HNSCC is rather limited, and progress against this disease has been difficult. Intergroup efforts may allow the execution of large, randomized trials that will improve the outcome of this devastating disease.

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PI3-Kinase: Genomics to Clinical Practice

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Targeting the PI3K Pathway in Head and Neck Squamous Cell Carcinoma

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OVERVIEW

Head and neck squamous cell carcinoma (HNSCC) is a heterogeneous disease arising from the mucosal epithelia in the head and neck region. The most common risk factors are tobacco use, alcohol consumption, and HPV infection, particularly in the oropharynx. The HPV-positive HNSCC is biologically and clinically distinct from the HPV-negative HNSCC; however, deregulations within the phosphatidylinositol 3-kinase (PI3K) pathway are frequent in both HPV-positive and HPV-negative HNSCC as it is the most frequently altered oncogenic pathway with a gain-of-function in HNSCC. This article reviews the basic biology and clinical data from the trials involving anticancer agents targeting the PI3K pathway in HNSCC. It also discusses the difficulties of translating the preclinical data to tangible clinical efficacy of these agents in patients with HNSCC even when there is significant preclinical data suggesting the PI3K pathway is a promising therapeutic target in HNSCC. We conclude that additional studies to determine appropriate patient selection for the activation of PI3K pathway and to develop targeted agents either as a monotherapy or combination therapy with favorable toxicity profiles are required before a broader clinical application.

Head and neck squamous cell carcinoma is a heterogeneous disease originating from the mucosal epithelia in the head and neck region, most commonly the oral cavity, oropharynx, hypopharynx, and larynx. The risk factors are tobacco use, alcohol consumption, and HPV infection, particularly in the oropharynx.[1,2] The HPV-positive HNSCC is now established as a separate entity with distinct clinical characteristics, including younger age of onset, better performance status, less smoking history, and its association with high-risk sexual behaviors compared to the HPV-negative HNSCC.[3,4] In addition, the HPV-positive HNSCC has a distinct molecular profile compared to the HPV-negative HNSCC, including lack of *TP53* and *CDKN2A* mutations; however, mutations or copy number variations of genes within the PI3K pathway are frequent in both HPV-positive and HPV-negative HNSCC as it is the most frequently altered oncogenic pathway with a gain-of-function in HNSCC.[5] This article reviews the basic biology and clinical data from trials involving the PI3K pathway inhibitors in patients with HNSCC.

BASIC BIOLOGY OF THE PI3K PATHWAY

P13Ks are divided into three classes: class I, II, and III. The differences in these classes are comprehensively reviewed by Thorpe et al.[6] Class I is further divided into subclass IA and

IB in mammals. Class IA PI3Ks are heterodimeric kinases consisting of a p110 catalytic subunit (p110-alpha, p110-beta, and p110-delta encoded by *PIK3CA*, *PIK3CB*, and *PIK3CD*, respectively) and a p85 regulatory subunit (p85-alpha and its splice variants, p55-alpha and p50-alpha, encoded by *PIK3R1*; p85-beta encoded by *PIK3R2;* and p55-gamma encoded by *PIK3R3*). These three p110 catalytic subunit isoforms can form a heterodimer with any of the five p85 regulatory subunits. Class IB PI3Ks are heterodimeric kinases consisting of a p110-gamma catalytic subunit encoded by *PIK3CG* and a p101 or p87 regulatory subunit encoded by *PIK3R5* and *PIK3R6,* respectively. Unlike class I PI3Ks, class II PI3Ks are monomeric lipid kinases without a regulatory subunit. There are three class II isoforms, including PI3K-C2-alpha, PI3K-C2-beta, and PIK3-C2-gamma encoded by *PIK3C2A, PIK3C2B,* and *PIK3C2G*, respectively. VPS34 is the sole Class III PI3K encoded by *PIK3C3* and forms a heterodimer with VPS15 encoded by *PIK3R4.*

Activation of the PI3K signaling pathway is highly regulated. PI3K activation is initiated by activated receptor tyrosine kinases such as ErbB family receptors, fibroblast growth factor receptors, insulin-like growth factor 1 receptor and others, as well as G protein-coupled receptors.[6,7] On activation, class I PI3Ks translocate to the plasma membrane where inhibition by the p85 regulatory subunit is relieved, and the p110 catalytic subunit catalyzes the phosphorylation

FIGURE 1. The PI3K Network

Class I PI3Ks are heterodimeric kinases consisting of a p110 catalytic subunit (class 1A-p110-alpha, p110-beta, and p110-delta, and class 1B-p110-gamma proteins) and a p85 regulatory subunit. PI3Ks are activated by receptor tyrosine kinases and GPCRs. PI3Ks phosphorylate PIP_2 to PIP_3, which functions as a second messenger. PIP_3 acts by recruiting downstream protein kinases, such as PDK1 and AKT, to the cell membrane that results in their activation. Subsequently, further downstream signaling network is activated and influence important cellular functions, such as cell proliferation, cell cycle, metabolism, and cell survival.

Abbreviations: 4EBP1, 4E binding protein 1; BCL-2, B-cell lymphoma 2; EEF2K, eukaryotic elongation factor-2 kinase; EIF4B, eukaryotic translation initiation factor 4B; ERK, extracellular signal-regulated kinase; FASL, Fas ligand; GPCR, G-protein coupled receptor; IRS1, insulin receptor substrate 1; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; PIP_2, phosphatidylinositol-4,5-bisphosphate; PIP_3, phosphatidylinositol-3,4,5-trisphosphate; PTEN, phosphatase and tensin homolog; RICTOR, rapamycin-insensitive companion of mTOR; RPS6, ribosomal protein S6; SGK3, serine/threonine-protein kinase 3; TSC, tuberous sclerosis protein.

of phosphatidylinositol 4,5-bisphosphate (PIP_2) to phosphatidylinositol 3,4,5-trisphosphate (PIP_3). In turn, PIP_3 acts as a second messenger and triggers AKT-dependent and AKT-independent signaling pathways (Fig. 1).[6-8] Activated AKT further phosphorylates downstream targets, including mammalian target of rapamycin (mTOR),[9] a master regulator of cellular proliferation, metabolism, and protein translation. Activation of the PI3K pathway is negatively regulated by a lipid phosphatase, phosphatase and tensin homolog (PTEN), which catalyzes the dephosphorylation of PIP_3 to PIP_2 and governs numerous cellular processes.[10] Although class I PI3Ks are extensively studied, physiological roles of class II and class III PI3Ks are poorly understood; therefore, they will

not be discussed in this review because they are beyond the scope of this article.

THE PI3K PATHWAY DEREGULATION IN HEAD AND NECK SQUAMOUS CELL CARCINOMA

With advancements in sequencing technology, HNSCC have been extensively sequenced through whole-genome sequencing, whole-exome sequencing, and targeted sequencing of cancer-related genes.[5,11-14] Collective data estimate the mutations and/or copy number variations of *PIK3CA* are detected in 32% of HNSCC (130/480 [27%] of HPV-negative and 63/171 [37%] of HPV-positive HNSCC).[14] Furthermore, a loss of *PTEN*, the PI3K negative regulator, also is frequently seen in patients with HNSCC, resulting in unrestrained activation of the pathway. Earlier studies showed 14% to 40% of patients with HNSCC to have *PTEN* loss of function because of a loss of heterozygosity or mutation, whereas recent tumor DNA sequencing studies show mutations or copy number variations in approximately 11% of HPV-positive and 5% of HPV-negative HNSCC.[14-16] When the mitogenic pathways (MAPK, JAK/STAT, and PI3K) relevant to HNSCC were evaluated, genes in the PI3K pathway were most frequently altered (30.5%).[17] In addition to the detectable genomic alteration by tumor sequencing, sufficient data suggest that deregulation of the PI3K pathway plays an important role in the development and metastasis of HNSCC associating with poor prognosis.[17-20]

For patients with HPV-positive HNSCC, recent studies also have demonstrated that epidermal growth factor recep-

KEY POINTS

· Deregulations within the phosphatidylinositol 3-kinase (PI3K) pathway are frequent in both HPV-positive and HPV-negative HNSCC.
· *PIK3CA* is the most commonly mutated oncogene in HNSCC.
· There are numerous clinical trials involving PI3K and mammalian target of rapamycin (mTOR) inhibitors, but clinical benefits of these agents in unselected patients with HNSCC are unclear.
· Predictive biomarkers of PI3K and mTOR inhibitor response are still under development.
· Further studies are required to develop the PI3K pathway targeted agents with favorable toxicity profiles.

tor (EGFR) and PI3K signaling are required for the viral entry into the cells that may be pertinent in this HNSCC subtype.[21,22] Pretreatment of patients with keratinocytes or cervical cancer cells in vitro with an EGFR inhibitor (gefitinib) and two different PI3K inhibitors (PI-103 and wortmannin) is sufficient to inhibit HPV-16 endocytosis and capable of preventing viral entry. In addition, PI3K/mTOR activation and suppression of autophagy in the early stages of patients with HPV16 infection are crucial for viral entry and infection.[22] Following HPV infection, the PI3K pathway appears to play an important role in established HPV-positive HNSCC as well. Gene-expression profile analysis of HNSCC has determined that HPV-positive HNSCC upregulates genes within the 3q26–29 chromosomal region, which is the locus containing *PIK3CA*. Further analyses by RT-PCR and reverse phase protein arrays confirm that *PIK3CA* is upregulated in patients with HPV-positive HNSCC compared to HPV-negative HNSCC.[20,23]

CLINICAL DEVELOPMENT OF PI3K INHIBITORS IN HEAD AND NECK SQUAMOUS CELL CARCINOMA

As *PIK3CA*, which encodes the catalytic subunit of PI3K, is overall the most frequently altered oncogene in human cancers, numerous PI3K-targeted agents currently are in clinical development. In a preclinical study using HNSCC patient tumor-derived xenografts (PDXs), PDXs harboring *PIK3CA* mutations were shown to be more sensitive to the PI3K and mTOR dual inhibitor, NVP-BEZ235, as compared with those lacking *PIK3CA* mutations.[17] Encouraged by the efficacy data seen in preclinical models such as these PDX studies, a number of clinical trials in patients with HNSCC currently are underway to evaluate the efficacy of small molecules that inhibit key points of this pathway (Table 1).

PI3K inhibitors are under evaluation as a monotherapy or in combination with previously established radiation and/or chemotherapy regimens in patients with HNSCC. PI3K inhibitors, such as buparlisib, BYL-719, or PX-866, are being investigated in phase II trials in patients with HNSCC in combination with chemotherapy or cetuximab. PI3K and mTOR share similarities in their kinase domain. Some compounds are developed to inhibit Class I PI3K isoforms, as well as mTORC1 and mTORC2, and many of these multikinase inhibitors are in clinical development (e.g., NVP-BEZ235).[24] However, although the biologic rationale is strong for the use of PI3K inhibitors, the efficacy of these agents presently is unclear in unselected patients with HNSCC. In a randomized phase II trial in recurrent and/or metastatic patients with HNSCC, PX-866 was administered with cetuximab, and it showed no evidence of clinically meaningful benefits.[25] Eighty-three patients were randomly assigned 1:1 to receive cetuximab once a week with or without PX-866; there were no complete responses. The objective response rates were 10% in the combination therapy and 7% in the cetuximab monotherapy, without any differences in disease control rates (55% vs. 56%), median progression-free survival (80 days for both groups), and overall survival (211 days in the PX-866 and cetuximab arm vs. 256 days in the cetuximab alone arm).

In addition, although there was no clear benefit of adding PX-866 in these previously heavily treated patients with HNSCC, the toxicities were more pronounced in the combination arm compared to the cetuximab alone arm. These toxicities included worse nausea (53% vs. 23%), vomiting (45% vs. 15%), fatigue (43% vs. 23%), diarrhea (40% vs. 21%), rash (45% vs. 31%), hypokalemia (25% vs. 10%), and dysphagia (18% vs. 3%). The clinical development of NVP-BEZ235 has been halted because of intolerable toxicities. For the further development, additional studies with appropriate patient selection with the activation of PI3K pathway and improved toxicity profiles are required.

Furthermore, numerous mTOR inhibitors also are being evaluated in patients with HNSCC. These mTOR inhibitors include everolimus and temsirolimus through phase II studies in neoadjuvant (or induction) chemotherapy and recurrent and/or metastatic settings. Rapamycin analogs, such as temsirolimus and everolimus, specifically inhibit mTORC1 and already are approved by the U.S. Food and Drug Administration in renal cell carcinoma, subependymal giant cell astrocytoma, pancreatic neuroendocrine tumors, and hormone receptor–positive, HER2-negative breast cancer in combination with exemestane in the United States.[26-30] In a phase II trial, a combination of temsirolimus and low-dose weekly carboplatin and paclitaxel was well tolerated in patients with recurrent and/or metastatic HNSCC.[31] When 30 patients were treated with the combination regimen, the overall radiological response rate was 43% with one complete response and 12 partial responses; median overall survival was 12.9 months. Overall, this regimen was well tolerated. The most common (greater than three) adverse events were neutropenia, dysphagia, and anemia. However, other combination trials evaluating temsirolimus and erlotinib in a similar recurrent and/or metastatic population of patients with HNSCC revealed intolerable toxicities such as fatigue, diarrhea, and infection, which resulted in early closure of the study.[32]

There are additional drugs that target other proteins within the PI3K pathway beyond PI3Ks and mTORs. Novel Akt inhibitors, such as MK2206, AZD5363, and GSK690693, are in development through phase I and II clinical trials.[33] Although it is not a direct inhibitor of mTOR, metformin, which is commonly used in type II diabetes, also is being investigated as an anticancer agent in patients with HNSCC.[34] Metformin indirectly inhibits mTORC1 by increasing intracellular adenosine monophosphate (AMP) levels mediated by AMP-activated protein kinase (AMPK)– dependent and independent mechanisms, and may play a role in management of HNSCC.[35,36]

ACTIVATION OF THE PI3K PATHWAY AS A BIOMARKER OF TREATMENT RESPONSE

Development of PI3K pathway inhibitors has not been straightforward because of the demonstrated lack of efficacy in unselected patient populations and unexpected degrees of

Table 1. Active Clinical Trials Evaluating PI3K/AKT/mTOR Targeted Agents in Patients with Locally Advanced, Recurrent, and/or Metastatic HNSCC*

Targeted Agent	Additional Targeted Agent	Additional Therapy	Inclusion Criteria	Phase	Clinical Trial Identifier
PI3K Inhibitor					
PX-866	-	Docetaxel	Recurrent or metastatic HNSCC/NSCLC	I/II	NCT01204099
PX-866	Cetuximab	-	Recurrent or metastatic HNSCC/CRC	I/II	NCT01252628
BYL-719	-	-	Recurrent or metastatic HNSCC	II	NCT02145312
BYL-719	Cetuximab	-	Recurrent or metastatic HNSCC	I/II	NCT01602315
BYL-719		Paclitaxel	Recurrent or metastatic HNSCC/BRC	I	NCT02051751
Buparlisib	-	-	Recurrent or metastatic HNSCC	II	NCT01527877
Buparlisib	Cetuximab	-	Recurrent or metastatic HNSCC	I/II	NCT01816984
Buparlisib	-	Paclitaxel	Recurrent or metastatic HNSCC	II	NCT01852292
Buparlisib	-	IMRT, cisplatin	Locally advanced HNSCC	Ib	NCT02113878
PI3K/mTOR Inhibitor					
NVP-BEZ235	-	-	Recurrent or metastatic solid tumors	I	NCT01343498
NVP-BEZ235	NVP-BKM120	Paclitaxel	Recurrent or metastatic solid tumors	I	NCT01285466
NVP-BEZ235	MEK-162	-	Recurrent or metastatic solid tumors	I	NCT01337765
NVP-BEZ235	Everolimus	-	Recurrent or metastatic solid tumors	I/II	NCT01508104
mTOR Inhibitor					
Everolimus	-	-	Recurrent or metastatic HNSCC	II	NCT01111058
Everolimus	-	-	Recurrent or metastatic HNSCC	II	NCT01051791
Everolimus	Cetuximab	Carboplatin	Recurrent or metastatic HNSCC	I/II	NCT01283334
Everolimus	Erlotinib	-	Recurrent or metastatic HNSCC	II	NCT00942734
Everolimus	Vatalinib	-	Recurrent or metastatic solid tumors	I	NCT00655655
Everolimus	-	IMRT, cisplatin	Locally advanced HNSCC	I	NCT00858663
Everolimus	-	Docetaxel, cisplatin	Locally advanced HNSCC	I	NCT00935961
Everolimus	-	Carboplatin, paclitaxel	Locally advanced HNSCC	I/II	NCT01333085
Everolimus	Cetuximab	Cisplatin, paclitaxel	Locally advanced HNSCC	II	NCT01133678
Temsirolimus	-	-	Recurrent or metastatic HNSCC	II	NCT01172769
Temsirolimus	-	Carboplatin, paclitaxel	Recurrent or metastatic HNSCC	I/II	NCT01016769
Temsirolimus	Cetuximab	-	Recurrent or metastatic HNSCC	II	NCT01256385
Temsirolimus	Cetuximab	Cisplatin	Recurrent or metastatic HNSCC	I/II	NCT01015664
Temsirolimus	Erlotinib	-	Recurrent or metastatic HNSCC	II	NCT01009203
Sirolimus	-	-	Recurrent or metastatic HNSCC	I/II	NCT01195922
Sirolimus	-	Grapefruit juice	Recurrent or metastatic solid tumors	I	NCT00375245
Ridaforolimus	Cetuximab	-	Recurrent or metastatic HNSCC/NSCLC/CRC	I	NCT01212627
Metformin	-	Paclitaxel	Recurrent or metastatic HNSCC	II	NCT01333852

Abbreviations: HNSCC, head and neck squamous cell carcinoma; IMRT, intensity modulated radiation therapy; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; BRC, breast cancer.
*All trial data are available at www.clinicaltrials.gov.

toxicity. Because of the ease of tumor DNA testing for *PIK3CA* mutations, many have proposed that the *PIK3CA* mutations are an integral biomarker for screening patient populations with PI3K pathway activation for future clinical trials.[37] Some studies suggest that patients with HPV-positive HNSCC would be more sensitive because of frequent *PIK3CA* mutations and enrich the trial.[17] However, in a recent study of cetuximab with or without PX-866, tumor HPV status was assessed by p16 immunohistochemistry.[25] Twenty-six patients (57%) of 46 with available tissue were HPV positive and 20 patients (43%) were HPV negative. There was no association between the tumor HPV status and

response. *PIK3CA* mutations were detected in 17% of patients, but no response was seen in these eight patients with the *PIK3CA* mutation-harboring tumors.

In addition, the PI3K pathway activation through compensatory receptor tyrosine kinase activation, such as MET and HER3, has been proposed as one of the resistance mechanisms of EGFR inhibitors in preclinical studies, suggesting PI3K/mTOR inhibitors may be developed in patients who are EGFR inhibitor–resistant in addition to patients with the *PIK3CA* mutations.[38,39] In a recent preclinical study, the combined activity of cetuximab and mTOR inhibitors in patients with HNSCC was evaluated. Cetuximab-sensitive

HNSCC cells were transduced to express *PIK3CA* and *RAS* oncogenes, and tumor xenografts were treated with control, cetuximab, or rapamycin. The in vivo study showed that patients with HNSCC tumor xenografts expressing mutant PI3K and Ras proteins relapsed a few weeks after the initial response to cetuximab treatments. However, the addition of rapamycin dramatically increased antitumor activity in these cetuximab-resistant tumors, supporting the rationale to evaluate a combination of cetuximab/mTOR inhibitors for treatment of patients with HNSCC.[39]

However, a vast majority of the model systems use the H1047R *PI3KCA* mutation that does not reflect the most commonly seen mutations.[5] For example, there are differences in the *PIK3CA* mutation hotspots between patients with HPV-positive and HPV-negative HNSCC. Greater than 90% of HPV-positive patients with HNSCC have mutations in the helical domain (i.e., E542K or E545K), whereas patients with HPV-negative HNSCC have mutations throughout the entire gene, although the hotspot mutations in the helical and kinase domains (i.e., H1047R) are relatively more frequent.[14] The site of the mutations and resulting amino acid substitutions might produce functionally different mutant proteins and further differ depending on the genetic background of patients with HPV-positive and HPV-negative HNSCC. These phenotypical differences may result in varied responses to the PI3K targeted agents and substantially affect the development of predictive biomarkers. This concern is validated in the PX-866 trial in which the *PIK3CA* mutations were not associated with response to cetuximab or cetuximab and PX-866 combination.[25] In addition, patients with HNSCC have *PTEN* loss and other functional gain or loss of genes/proteins within the pathway that may affect the pathway in the absence of the *PIK3CA* mutations.[14] The functional significance of these features must be adequately characterized before applying them to clinical trials.

CONCLUSION

Advancements in genomic and proteomic technology are providing a glimpse of the complexity of cancer biology and generating rich hypotheses for potential therapeutic targets. In addition, respective companion diagnostic biomarkers are being developed for clinical application. Currently, a large body of preclinical data indicate the PI3K pathway is important and a promising therapeutic target in patients with HNSCC. However, they have not always translated to clinically meaningful efficacy in clinical studies. Additional studies to determine an appropriate method of patient selection with the activation of PI3K pathway and to develop targeted agents with favorable toxicity profiles are required. Existing data on *PIK3CA* mutations as a predictive biomarker to PI3K/mTOR inhibitor response or the EGFR inhibitor resistance are not yet fully developed. Potential differences in the gene/protein function based on the location and amino acid changes resulting from the *PIK3CA* mutations in appropriate genetic context of other coexisting pathologic signaling network, must be delineated further before proceeding with a broader clinical application.

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HEALTH SERVICES RESEARCH AND QUALITY OF CARE

Introduction to Methods in Comparative Effectiveness Research

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Comparative Effectiveness Research in Cancer with Observational Data

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OVERVIEW

Observational studies are increasingly being used for comparative effectiveness research. These studies can have the greatest impact when randomized trials are not feasible or when randomized studies have not included the population or outcomes of interest. However, careful attention must be paid to study design to minimize the likelihood of selection biases. Analytic techniques, such as multivariable regression modeling, propensity score analysis, and instrumental variable analysis, also can also be used to help address confounding. Oncology has many existing large and clinically rich observational databases that can be used for comparative effectiveness research. With careful study design, observational studies can produce valid results to assess the benefits and harms of a treatment or intervention in representative real-world populations.

Comparative effectiveness research increasingly is being recognized as a priority area in cancer research. Although researchers have been conducting comparative effectiveness research for decades, this area of research achieved national prominence when, as part of the American Recovery and Reinvestment Act of 2009, $1.1 billion was allocated to comparative effectiveness research. Shortly thereafter, the Patient Protection and Affordable Care Act of 2010 established the Patient-Centered Outcomes Research Institute (PCORI). The mandate of PCORI is "to improve the quality and relevance of evidence available to help patients, caregivers, clinicians, employers, insurers, and policy makers make informed health decisions. Specifically, we fund comparative clinical effectiveness research, or CER, as well as support work that will improve the methods used to conduct such studies."[1] These initiatives have stimulated interest and provided new funding opportunities in comparative effectiveness research.

The Institute of Medicine has formulated a definition of comparative effectiveness research as follows: "CER is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels."[2] Thus, comparative effectiveness research is meant to compare the risks and benefits of a given approach in a real-world heterogenous population with the ultimate goal of improving health care decisions and out-

comes. Comparative effectiveness research encompasses a broad array of study types, including randomized trials (pragmatic clinical trials, cluster-randomized trials, adaptive trials), research synthesis (systematic reviews, meta-analysis, decision analysis), and observational studies (cohort, case-control, cross-sectional designs).

Randomized trials have long been considered the gold standard when evaluating the efficacy of a particular intervention. These studies test the effect of an intervention under carefully controlled conditions and are the gold standard to evaluate the efficacy of a particular intervention. Although randomized trials have the best internal validity, the generalizability of results can be limited because of strict eligibility criteria. Clinical trial participants tend to be systematically different than patients in the general population, with younger ages and fewer concurrent medical conditions.[3] Pragmatic clinical trial designs address some of these issues, but randomized trials remain expensive and time consuming. Observational studies increasingly are being used to evaluate the effectiveness of treatments in real-world populations, because they can address the gaps in randomized studies and the benefits in patient populations who were not included in the clinical trials. In addition, observational studies can be conducted with a relatively low cost and often include large numbers of representative populations.

ROLE OF OBSERVATIONAL STUDIES

The Effective Health Care website has published a guide for methods in comparative effectiveness research.[4] This article

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provides a conceptual framework for the use of observational studies in comparative effectiveness research. The authors note that researchers should ask two key questions before undertaking an observational CER study: (1) Are there gaps in the evidence from randomized controlled trials? and (2) Will observational studies provide valid and useful information?[4]

When data are available from randomized clinical trials, observational studies may provide little additional information. However, at times, randomized clinical trials may not be possible. Studies of medications, particularly if they are off patent, may have no financial support. In some situations, random assignment may not be feasible or ethical. For instance, studies of a rare cancer may never be able to accrue a sufficient number of patients to obtain statistically valid results. Trials may be unethical to conduct in situations when there is not clinical equipoise between the two therapeutic options. Even in situations when clinical trials may be possible, existing clinical trials may not be relevant to the population of interest or may not include the outcomes of interest. This situation often arises when evaluating the benefit of a treatment for patients who are older or who have many comorbid conditions. Randomized trials often focus on short-term outcomes and may not have sufficient follow-up times to evaluate late outcomes of interest. For example, clinical trials for patients with breast cancer typically have not observed patients to assess the risks of long-term outcomes, such as congestive heart failure related to anthracyclines or myocardial infarction as a result of radiation therapy, both of which may occur decades after treatment. In these situations, when no randomized studies exist, the trials were not conducted in the population of interest, or the studies do not capture the endpoint of interest, observational studies can be used to fill in the gaps in data.

The second question to ask before undertaking an observational study is whether an observational study can provide valid information.[4] The major challenges in observational studies are assessing and addressing the risk of bias, particularly the risk of selection bias. Selection bias refers to systematic differences in the risk of the outcome between the two compared groups of patients. For instance, in a comparison of the effectiveness of chemotherapy, selection biases could work in several ways. First, patients who have high-risk disease features, such as higher-stage disease or high-grade tumors, would be more likely to be treated with chemotherapy.

This selection bias could cause the chemotherapy-treated group to appear to have a worse outcome, simply because they had higher-risk disease. Many of these high-risk features can be measured and adjusted for in analyses, but some high-risk features, such as positive margins or lymphovascular invasion, may not be routinely captured or reported in national databases. A second way in which selection biases can work is that patients who are older or who have poorer performance statuses and more comorbidities will be less likely to be treated. This selection bias would result in the untreated patients appearing to have worse outcomes, simply because of poorer health at diagnosis. Again, some of these predictors of treatment, like age, can be measured and adjusted for in statistical models. However, other important factors that clinicians use to decide treatment, like performance status or frailty, are not routinely captured in databases. These factors can act as unmeasured confounders, which are extraneous variables that are associated with both the independent variable and dependent variable. For instance, performance status is associated with both the likelihood of treatment and survival and could lead to biased estimates of the efficacy of treatment. Another illustration of selection biases can be seen in an example of evaluating the benefit of treatment for patients with prostate cancer.[5] In an analysis of older men with early-stage prostate cancer, the use of any active treatment (radiation or surgery) was associated with better survival after adjustment for all measured covariates.[5] When evaluated by cause of death, treatment was associated with improved overall survival and improved prostate cancer–specific survival. However, prostate cancer treatment also was associated with better cause-specific survival from cardiovascular disease, pneumonia, and diabetes. There are no plausible mechanisms by which treatment for prostate cancer could affect survival from diabetes, other than through confounding from underlying health. This example illustrates the challenges of identifying and accounting for selection biases. Selection biases also can result in confounding by indication. Confounding by indication can occur when the patients who are prescribed a particular treatment differ from those who are not prescribed a given treatment because of the medical indication for which the drug is prescribed. Many other biases can occur in observational studies, such as performance bias (e.g., difference in adherence), detection bias (e.g., differential assessment of outcomes), and outcome-reporting bias.[4] Before undertaking an observational analysis, careful consideration must be given to the possibility of bias and how potential biases could affect the results.

ANALYTIC TECHNIQUES

Several approaches can be taken to address bias in observational studies. Most studies will use multivariable regression analyses to adjust for confounders and to address issues related to nonrandom treatment assignment. This method can provide statistical adjustment for all measured variables but cannot adjust for unmeasured confounders. Propensity score analysis is another approach to improve the balance of un-

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KEY POINTS

- Observational studies are particularly useful when randomized studies are not feasible or have not included the population or outcome of interest.
- Selection biases are the primary threat to validity of observational studies.
- Multivariable regression models, propensity score analyses, and instrumental variable analyses can be used to help address selection biases and confounding.

measured confounders between the two experimental groups. In propensity score analysis, multivariable regression is used to calculate the propensity of receiving the intervention of interest. This propensity score then can be entered as an explanatory variable in the regression models or can be used for matching. Some studies have suggested that propensity score stratification can remove more than 90% of the bias in observational studies.[6] Another approach is the use of instrumental variable analysis, which is a method used in econometrics. An instrumental variable is a variable that is strongly correlated with the treatment or intervention but without any independent effect on the outcome. An appropriate instrumental variable can help address unmeasured confounding. In oncology studies, distance to the treatment center and regional treatment rates have been used as instruments.[7-9] However, finding an appropriate instrumental variable can be challenging.

TYPES OF OBSERVATIONAL STUDIES

Several different study designs, such as cross-sectional, cohort, and case-control designs, can be used for observational research. A cross-sectional study is a study in which the prevalence of the exposure and outcome are measured at the same point in time. In this design, participants are identified independent of exposure and outcome. Cross-sectional studies can evaluate prevalence but cannot measure disease incidence. In a cohort study, participants are identified by their exposure and then observed over time for the outcome of interest. For instance, patients with breast cancer who were and were not treated with trastuzumab could be observed for the risk of congestive heart failure. A cohort study allows for the calculation of incidence in treatment groups. When they are prospectively designed, these studies may need an impractically large sample size if the outcome is not common. Large, retrospective, cohort studies using existing national databases get around this limitation with their large size and lengthy follow-up times. A third common study design is a case-control study. In this study design, cases and controls are identified by the outcome of interest, and then the prevalence of exposure is compared. In the example of trastu-

zumab cardiotoxicity above, patients with heart failure would be identified and then compared by exposure to trastuzumab. Other study designs, such as case cohorts or case crossovers, also may be used but are beyond the scope of this review.

SAMPLE DATA SOURCES IN ONCOLOGY

Oncology has a long track record of observational studies, in part because of the high-quality data provided by cancer registries. Incident cancer cases are reported to state cancer registries, which track cancer incidence, staging, first course of treatment, and outcomes. Cancer registries have provided data for numerous research studies and also have been linked with other databases. Commonly used observational data sets for cancer research are described below and are summarized in Table 1.

Surveillance, Epidemiology, and End Results

The Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) collects and complies data from cancer registries to provide information on cancer incidence and survival in the United States. This program was started in 1973 and has expanded over the years to include data from 10 states (Connecticut, Hawaii, Iowa, New Jersey, New Mexico, California, Virginia, Kentucky, Louisiana, and Utah), six metropolitan areas defined by county borders (Atlanta, Detroit, Los Angeles, San Francisco/Oakland, San Jose/Monterey, and Seattle/Puget Sound), the supplemental SEER registries of[4]Alaska Natives, Arizona Native Americans, and Cherokee Nation, and 10 counties in rural Georgia.[10] These SEER registries cover approximately 28% of the U.S. population.[10] For each patient with an incident cancer, the following information is reported: (1) demographics: case number, age, sex, race/ethnicity, state and county of birth, state and county of residence, date and cause of death according to death certificate (of note, cancer recurrence is not captured); (2) cancer: type, month and year of diagnosis, diagnostic confirmation, and laterality; (3) extent of disease: American Joint Committee on Cancer (AJCC) stage, historic SEER stage, tumor size and extension, number

TABLE 1. Data Sources

Data Set	Type of Data	Years Available with Incident Cases	Population
SEER	Cancer registry	1973-2013	All incident cancer cases in SEER regions
100% Medicare	Health care claims	Through 2012	Age > 65, disabled, end stage renal disease
SEER-Medicare	Registry-linked claims	1973-2011	Age > 65, disabled, end stage renal disease
SEER-MHOS	Registry-linked to survey	1998-2011	Age > 65
SEER-NLMS	Registry-linked to survey	1979-2011	All ages
HCCI	Health care claims from United, Aetna, Humana, and Kaiser	2009-2013	All; employees, spouses, dependents
Marketscan	Health care claims from 45 large employers	2003-2013	All; employees, spouses, dependents
NCDB	Clinical database	Since 1985	All ages; patients treated at CoC accredited facilities

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; MHOS, Medicare Health Outcomes Survey; NLMS, National Longitudinal Mortality Study; HCCI, Health Care Cost Institute; NCDB, National Cancer Database; CoC, Commission on Cancer.

of lymph nodes examined, number of positive lymph nodes, histologic grade, histologic type; and (4) treatment: type of surgery and radiotherapy for first course of treatment. These data provide a definitive source of information on cancer incidence, staging, and survival. The information on treatment is less complete. In general, the ascertainment of surgery by registries is the highest-quality treatment variable. The use of radiation therapy may be under-ascertained by registries. In the case of breast cancer, the under-ascertainment has been reported to be differential by age, income, and other treatment.[11,12] Complete information on chemotherapy administration is difficult to capture; thus, rates of chemotherapy use are not reported in the SEER database. The SEER database is de-identified, publically available, and free of charge.

Medicare

Medicare is the primary health insurer for 97% of the U.S. population age 65 and older. The Medicare Claims Data System collects information on all services provided to Medicare beneficiaries under its hospital (Part A), supplemental (Part B), and prescription drug (Part D) insurance plans. Part A covers inpatient hospitalizations and care in skilled nursing homes, whereas Part B covers physician services; hospital outpatient services; durable medical equipment; home health services; and other outpatient medical services, such as diagnostic x-rays and laboratory tests. Part D data includes information on prescription drug use and has been available since 2006. The unlinked Medicare data are comprised of enrollment files and health care claims. These data do not have information on the dates of diagnosis, stage, histology, or recurrence, and this lack of registry data has limited the use of the unlinked Medicare files for cancer research. For several cancer types, such as breast cancer, validated algorithms have been developed to identify incident cases.[13] The strength of these data is in studies of patterns of care, geographic variation, and costs of therapy. To obtain the data set with identifiers, an application should be submitted to the Research Data Assistance Center (ResDAC). The cost is dependent on the specific data request.

SEER-Medicare Linked Database

Under an agreement between the NCI and the Centers for Medicaid & Medicare Services (CMS), patients in the SEER database who are eligible for Medicare have been linked with their Medicare records. Of persons who are reported by SEER as diagnosed with cancer at age 65 or older, 93% were matched with their Medicare enrollment records.[14] At present, patients with cancer who were diagnosed through 2011 are linked, and their Medicare claims are available through 2012. For patients with cancer in the SEER database, Medicare enrollment and eligibility information and a subset of SEER data are in the Patient Entitlement and Diagnosis Summary File (PEDSF). The PEDSF also contains census-tract–level information, including ethnicity, education, income, percentage English-speaking residents, and population density. In addition to the registry data provided by SEER, these data include all billing claims for each patient. The claims can

supplement data from the SEER registry and provide information on diagnostic testing and additional treatment information, such as chemotherapy use and patterns of surveillance. In addition, the data can be linked to the Area Resource File and the American Medical Association's Physician Masterfile, which can provide additional information about health resources and physician characteristics, respectively. These data do have some substantial limitations. First and foremost, these data are administrative data generated for billing, so they lack the detail of clinical data. The claims are only complete for those patients in the fee-for-service plans (rather than in the HMO plans) and do not capture services provided by the U.S. Department of Veterans Affairs. Finally, as with the SEER data, cancer recurrences are not captured. To obtain these data, an application must be submitted to the NCI for review. Cost estimates can be found on the SEER-Medicare website.[15] All publications resulting from these data must be reviewed before publication to ensure that patient confidentiality is protected.

SEER-Medicare Health Outcomes Survey Linked Database

The SEER–Medicare Health Outcomes Survey (MHOS) data set is a linkage of two large population-based databases. The SEER database, described above, has been linked with the MHOS, which is a large survey of health-related and quality-of-life information among participants in the Medicare Advantage Organization. These data include information on 12 cohorts of baseline and follow-up surveys at 2 years, which were conducted between 1998 and 2011.[16] Collected data include patient demographics, marital status, income, smoking status, chronic conditions, and health-related quality of life. From 1998 to 2005, the MHOS used the 36-question short-form (SF-36) to collect data on health-related quality of life, but the MHOS switched to the Veterans RAND 12-item health survey (VR-12) in 2006. This data set provides additional patient-reported information to the SEER data. However, the survey was not limited to participants with cancer nor timed with a diagnosis of cancer, therefore the small sample sizes may limit potential analyses.

SEER-National Longitudinal Mortality Study Linked Database

The National Longitudinal Mortality Study (NLMS) is a data set that includes sociodemographic data collected by the Census Bureau by in-person and telephone interviews, and it includes cause of death information. The variables include race/ethnicity, education, income, employment, occupation, smoking, health status, and health insurance status. These data have been linked with SEER and with Medicare claims and can be used in studies evaluating socioeconomic determinants of cancer and cancer outcomes or outcomes related to income or employment, in addition to other uses.

Commercial Claims Databases

There is an increasing number of databases that can be licensed for research on the commercially insured population.

These databases are analogous to the unlinked Medicare data, in that they are health care claims without linkage to cancer registry data. They lack information on cancer incidence, stage, or survival, but they can provide detailed treatment information on younger, privately insured patients. One of the most commonly used data sets is Marketscan data, which consist of proprietary data sets licensed by Thomson Medstat Inc. The data undergo internal quality checks for reasonableness of data and validity before they are released, and they are HIPPA compliant. Marketscan is a large nationwide employment-based database that contains information on medical claims and outpatient prescription drug claims for employees and their spouses and dependents; the data represent claims from approximately 45 large employers, and Marketscan captures insurance claims data from over 100 payers. All files of claims data can be linked to the enrollment file via de-identified person identifiers. These data represent the medical experience of insured employees and their dependents for active employees, early retirees, COBRA continuees, and Medicare-eligible retirees. The specific demographic covariates available through Marketscan include patient age and sex, birth year, marital status, and three-digit zip codes. Information on race and ethnicity is not available.

The Health Care Cost Institute (HCCI) is another source of data on the commercially insured population. The HCCI is a nonprofit organization founded by academic economists to create a comprehensive source of information on health care activity and costs. Their research database covers about 40 million people, which represents approximately one-quarter of the population covered by employer-sponsored insurance. The data set contains claims from Aetna, Humana, Kaiser Permanente, and United Healthcare. The data capture complete payment information, including payments from both the benefit plan and patient. Pharmacy and mail-order prescriptions are included. Other proprietary claims data include IMS LifeLink data, Perspective, and Optum Insight. These data sets can provide comprehensive information on younger, privately insured patients. However, these data sets also have some limitations beyond the lack of linked registry data. The continuous coverage in these data sets tends to be short, so longitudinal studies can be challenging. In addition, no information on survival is available, and thus long-term outcomes cannot be assessed.

National Cancer Database

The National Cancer Database (NCDB) is a clinical oncology database jointly sponsored by the American College of Surgeons and the American Cancer Society. This database collects information from hospital registries that are Commission on Cancer (CoC)-accredited facilities. This includes more than 1,500 hospitals in the United States and Puerto Rico. The database is quite extensive and covers approximately 70% of newly diagnosed cancer cases in the United States.[17] The data include information on patient characteristics, pathology, stage, prognostic factors, treatment, and outcomes. The strength of these data is the collection of clinically rich information, but the generalizability is somewhat limited because the data are not population based.

CONCLUSION

In summary, observational data can be a powerful resource for comparative effectiveness studies in cancer research. Observational studies are particularly useful to fill in gaps in data from randomized studies or when randomized studies cannot be conducted. Researchers must be cognizant of the risk of selection biases and confounding in observational research and must design studies carefully to minimize the risk of bias. The Agency for Healthcare Research and Quality's Effective Health Care Program has provided a checklist for considerations in study design when observational comparative effectiveness studies are proposed.[4] Given careful and thoughtful study design, observational studies can provide important and clinically relevant comparative effectiveness information in real-world populations. Finally, with the increasing use of electronic medical records and the ability to access large national data sets, this area of research is likely to continue to grow in scope and impact.

Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

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HEALTH SERVICES RESEARCH AND QUALITY OF CARE

Let the Sunshine In: Industry's Impact on Oncology Research and Practice

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The Impact of Industry on Oncology Research and Practice

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OVERVIEW

Public scrutiny has increased over potential conflicts of interest among oncology researchers and providers. Given the increased prevalence and complexity of industry relationships, oncologists are increasingly faced with ethical challenges when navigating their financial relationships with industry. Oncologists are continually dealing with changing conflict of interest policies within academic centers and professional societies. With the recent passage of The Sunshine Act, oncologists are beginning to understand the repercussions of this new law. The consequences of the increasing use of direct-to-consumer advertising on patients with cancer are also unclear. Finally, industry's perspective on the evolution of these relationships is not clearly understood. This manuscript discusses issues related to industry's influence on oncology practice and research.

Financial relationships between industry and oncology physicians and researchers are common. These relationships consist of research support, consultative fees, honoraria, and gifts. Recently, public scrutiny has increased about potential conflicts of interest that could arise in the oncology community. Given the increased prevalence and complexity of industry relationships, oncologists are increasingly faced with ethical challenges when navigating their financial relationships with industry.

Recent attention has been focused on physician–industry relationships in the wake of the Sunshine Act. Oncology researchers are forced to keep up with continual revisions of conflict of interest policies within academic centers and professional societies. The effect of the rise in direct-to-consumer advertising (DTC) on patients with cancer is also unclear. DTC advertising results in multiple ethical challenges since physicians are unable to function as unbiased intermediaries between patients and industry.

Industry's effect on physicians and patients with cancer is multidimensional and becoming increasingly complex. Patient and public reaction to these developments necessitate education and clarification of these complex issues. We will explore some of the issues relating to the effect of industry on oncology research and practice in the modern era.

FINANCIAL CONFLICTS OF INTEREST

Financial relationships between the pharmaceutical industry and oncology are common and increasing over time.[1-3] A cross-sectional survey of cancer clinical trials and editorials conducted in 2005 revealed that 44% of clinical trials were entirely or partially funded by industry.[4] Another study reported that 23% of all abstracts and 60% of plenary session abstracts from 2004 to 2005 at the American Society of Clinical Oncology (ASCO) Annual Meeting reported at least one author with an financial conflict of interest (FCOI).[2] A more recent analysis of ASCO Annual Meeting abstracts from 2006 to 2011 reported that 36% of all abstracts had at least one FCOI and that abstracts with FCOIs were featured at more prominent sessions at the Meeting.[5] These data demonstrate the increased influence of industry in oncology research and practice.

In the past, arguably the most prominent cancer research was funded by the federal government in the form of cooperative group studies. However, in recent years, there has been a shift toward industry-funded trials leading to the development and approval of cancer therapeutics. Modern cancer research has increasingly relied on efficient conduct of clinical trials using the newest anticancer therapeutic agents. Therefore, cancer researchers have formed increasing ties to industry given their access to research infrastructures and novel therapeutic agents.

The increasing relationship between industry and oncologists leads to both positive and negative consequences.[6,7] On the positive side, close collaboration between biomedical researchers and industry has undeniably facilitated the development of many new medical therapies.[8] Developmental therapeutics is an area in which key interests of the oncology researcher, patient, and industry are aligned. The patient community seeks effective new therapies, biomedical researchers and oncologists wish to translate basic discoveries into treatments, and industry wishes to develop new products.[9] However, as oncology researchers work more closely with industry, questions arise whether financial compensa-

tion and academic advancement may lead to unethical behavior. The presence of financial interests might influence decision making and research conduct. These relationships have the potential to compromise research integrity, create scientific bias for researchers, and lead to public and patient mistrust. Profit motives by the manufacturer, shared with the clinical researcher through FCOI, could potentially lead to poor or inaccurate science and ultimately harm the public interest.[10]

To date, management of FCOI has been based on rules or policies mandating disclosure of industry relationships. These policies aim to increase transparency to engender public trust for the medical research community, and by acknowledging the presence of these relationships, they ideally lead to an open dialogue between the public and oncologists. As policies call for wider disclosure of potential FCOI, and at times prohibition of specific financial relationships, there is both a need and an opportunity to better understand the prevalence of investigator and research relationships with industry and the effect of these relationships on research and dissemination of results.[6,7] However, despite the widespread implementation of conflicts of interest policies in academic centers, federal agencies, and professional medical societies, little is known about how FCOI influences research conduct, outcomes, and dissemination.[11-13]

These conflict of interest policies also do not address nonfinancial conflicts of interest that address professional or ideologic issues, such as academic advancement, promotion, and publication. The desire for academic advancement could lead academic cancer researchers to seek out relationships with industry that has proprietary technology in an effort to participate in more important and influential research. These nonfinancial conflicts have not been as well studied. Greater examination of the benefits and risks of these relationships should be paid.

Currently, most FCOI policies rely on disclosure alone to address conflicts of interest. In part because of the difficulty of relying on disclosure alone to address the problematic con-

sequences of physician–industry ties and associated conflicts of interest, proposals have emerged for academic medical centers to ban all gifts, meals, payment for travel to or time at meetings, and payment for participation in online continuing medical education (CME) from industry to physicians.[14] These concerns have also led to the consideration of creative ways to introduce more distance into relationships between physicians and industry, including provision of vouchers rather than samples for low-income patients, elimination of direct funding of CME, and limitation of grants for general support of research to institutions rather than individual physician investigators. Unfortunately, some conflicts of interest may be particularly hard to eradicate, including situations where physicians have an ownership interest in medical equipment being advertised. Nevertheless, it is clear that at least for relationships with manufacturers of drugs, tests, and technologies used in the management of patients with cancer, approaches that minimize the direct relationship and try to maintain some distance between individual physicians and industry merit consideration.

Given the complexity of these relationships with industry that lead to positive and negative consequences for the oncology provider and researcher, the oncology community must rationally understand these issues. It may be within the public interest to foster, rather than discourage, some relationships. Instead, there may be a need for greater scrutiny on the degree to which FCOI are managed or prohibited and the effect of such policies over time.

SUNSHINE ACT

The direct goal of the Sunshine Act is to enhance transparency about relationships between health care providers and purveyors of health care products and services. When the original bill was first introduced in 2007 (S.2029), one of the cosponsors, Senator Claire McCaskill, stated, "I believe that by bringing light to these relationships, this legislation will go far in reducing big drug companies' influence on the business of medicine." Another cosponsor, Senator Charles Schumer, stated, "This bill will shine a much needed ray of sunlight on a situation that contributes to the exorbitant cost of health care. Patients have the right to know if drug and device makers are attempting to influence physician prescribing decisions with gifts, consultations, and travel." Thus, the Sunshine Act requires companies to submit information regarding their financial relationships with providers to the U.S. Department of Health and Human Services (HHS) and for such information to be publicly available. This led to the creation of a database, Open Payments, so that patients can theoretically identify providers whose professional judgment may be clouded by personal financial interests, enabling informed patients to question their physicians' prescribing decisions. Furthermore, particularly concerned patients could simply choose physicians who had no financial relationships, based on a search of the Open Payments database.

It is too soon to assess whether or not patients are utilizing the Open Payments database in the manner Congress in-

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KEY POINTS

- Financial relationships between industry and oncology physicians are common.
- Conflict of interest policies historically have relied on disclosure to maintain transparency, but little is known about the effect and influence of these relationships on research conduct, outcomes, and dissemination.
- The goal of the Sunshine Act is to enhance transparency about these relationships, but its implementation has raised multiple concerns.
- Direct-to-consumer advertising has a substantial effect on medical practice and influences drug utilization.
- Partnerships between pharmaceutical companies and oncology researchers are essential for the development of new treatments and innovations.

tended. However, there are both direct and indirect negative consequences to physicians and teaching hospitals as a result of the Sunshine Act. Although the direct financial costs to physicians and teaching hospitals were estimated to be relatively modest ($250 and $3,500 for the first year, respectively), the potential for indirect costs from stigmatization of physicians and/or teaching hospitals cannot yet be assessed.

There is no question that some medical decisions are motivated by physicians' associations with manufacturers of pharmaceuticals and devices, but there are also many legitimate and beneficial relationships between physicians and industry, particularly in the context of research and development of investigational products. In fact, if Americans wish to have access to such investigational products, financial relationships between American physicians and industry are necessary. Notably, the implementation of the Sunshine Act does attempt to differentiate financial relationships associated with research from those associated with inducement of prescribing (e.g., speakers bureaus). However, the problematic implementation of the Open Payments database has led to significant concerns about the validity of the data. Furthermore, physicians must access the database to assess the validity of submitted data (and have the option to dispute specific entries)—potentially a substantial implementation cost. (As an example, one of the authors of this manuscript spent multiple hours working directly with the Open Payments database developers to gain access to his own data, as the record associated with his National Provider Identifier number had been inadvertently duplicated, thereby blocking access.)

The Open Payments website provides a guide for patients that distinguishes the different types of potential financial relationships of their physicians.[15] These include consulting fees, "compensation for services other than consulting, including serving as faculty or as a speaker at an event other than a continuing education program," honoraria, gifts, entertainment, food and beverage (exceeding $10 per year), travel and lodging, education (including reprints of journal articles and even if not requested by the physician), research, charitable contributions, "royalty or license," "current or prospective ownership or investment interest," "compensation for serving as faculty or as a speaker for an unaccredited and noncertified continuing education program," "compensation for serving as faculty or as a speaker for an accredited or certified continuing education program" (but only if the company recommends the speaker), grant (payments in support of a specific cause or activity), and "space rental or facility fees."

Of significant concern is the requirement for companies to report all indirect payments, specifically financial support to third parties (e.g., Conquer Cancer Foundation) who then utilize a peer review process to allocate funds to grantees. In this context, the Conquer Cancer Foundation website contains the following language as a warning to applicants: "This grant receives support that may result in a report to the Centers for Medicare & Medicaid Services (CMS) Open Payments website under the Physician Payments Sunshine Act. The supporting companies are required to report the amount

of the grant, the names of physicians who are awarded this grant, and the names of their institutions. This information may appear on the Open Payments website." Presumably, this would dissuade at least some qualified applicants from applying for grants, given concerns about the potential stigmatization associated with a successful application.

Another area of concern to researchers is companies' variable interpretation of the CMS Final Rule in regard to requirements to report potential "transfers of value" (TOVs) in the context of research publications (e.g., abstracts, presentations, original research articles). As clinical research is uncommonly conducted at single institutions, investigators must rely on companies for the organization and primary analysis of results. In addition, many companies utilize professional medical writers and graphic artists (either employees or contractors) to assist in the preparation of abstracts, presentations, and original research articles. Thus, many companies have interpreted the requirement to report publication support as a transfer of value to individual physicians, even though such publications may primarily benefit the company.[16,17]

Given the interests of Congress to both improve health and reduce health care costs, it is important to ask whether or not the Sunshine Act's implementation challenges outweigh the potential gains. In fact, patients may be less troubled by the financial relationships of their physicians than Congress. In one study of 102 patients with advanced cancer, the majority of patients were not concerned about financial relationships between their physicians and industry but were concerned about potential intrinsic nonfinancial interests.[18] Specifically, patients were concerned about their physician being promoted or becoming famous because of their participation in such research studies. So, if potential physician fame (rather than fortune) is of highest concern to patients, then the achievement of financial transparency may have little effect on direct interactions between patients and physicians in the context of prescribing decisions.

In contrast, Congress has never expressed concern about physician activities aimed at fame, although often fame begets fortune, particularly if the famous physician leaves the practice of medicine. Furthermore, a recent study showed that approximately one-half of the medical recommendations made by one set of famous physicians—those on medical talk shows— had either no evidence or were contradicted by the best available evidence, and they were rarely accompanied by any disclosure of financial interests.[19] It is unclear whether or not Congress has ever considered regulating medical recommendations made on talk shows. This may be of relatively little concern to HHS, since many of these recommendations relate to medical interventions not covered by Medicare or Medicaid.

Of greater concern is Congress's failure to strengthen the regulations and/or eliminate direct-to-consumer advertising of medications, since patients may seek inappropriate medications based on seeing (or hearing) such advertisements.[20] Although such advertisements are regulated in theory by the U.S. Food and Drug Administration (FDA), their enforcement

has been "lackadaisical."[21] Notably, the United States is one of only two countries in the world that permits such advertising. Furthermore, a recent paper from the other country that permits such advertising—New Zealand— calls for that country's policy to be reviewed, since such advertising "exposes patients to unnecessary adverse effects and iatrogenic harm, and increases costs for the health care sector through the prescription of expensive branded medication."[22]

Although direct-to-consumer advertising may be protected by a constitutional right to free speech in the United States,[23] the U.S. Constitution would presumably not prohibit requirements analogous to those included in the Sunshine Act and the Final Rule regarding transparency reports of relationships between companies and health care providers. For example, Congress could require public dissemination (e.g., in a database) of the costs of drugs marketed directly to consumers, as well as the overall costs of the marketing and advertising of such drugs. In addition, Congress could also require that all print ads aimed at a consumer audience include detailed information about drug costs, given the increasing importance of financial toxicity related to expensive drugs.[24] Similarly, television and radio ads could also be required to devote adequate time (e.g., 15 seconds) to discussing this increasingly important issue, with the goal of reducing demand for expensive drugs that may be only marginally better than much cheaper alternatives.

DIRECT-TO-CONSUMER ADVERTISING

Since 1962, the FDA has had regulatory authority over prescription drug advertising.[25] Although professionals have historically been the primary target of advertisements, DTC advertising began as early as the 1980s, primarily in print form. DTC advertising expanded dramatically after 1997, when the FDA issued draft guidance on broadcast advertisements[26] that was later finalized in 1999.[27] Industry spent approximately $150 million on DTC advertising in 1993, which rose to $1.1 billion by 1997, reached $3.2 billion by 2003, peaked at $4.9 billion in 2007 (also the peak of overall promotional spending for pharmaceutical products), and was $3.9 billion in 2011.[28,29]

DTC advertising has substantial influence on medical practice and affects drug utilization.[30-34] A public survey revealed that 30% of respondents had initiated conversations with their physicians about a medicine they saw advertised, and, of these, 44% reported actually receiving a prescription for the drug as the outcome of the conversation.[35] Many DTC advertisements target patients with cancer,[36] and a survey found that 86.2% of oncology patients reported awareness of such ads.[37] In another survey, 94% of oncology nurse practitioners reported having received medication requests prompted by DTC ads, and 40% indicated that they received one to five such requests per week.[38] DTC advertising relevant to oncology extends well beyond the marketing of prescription drugs, to include advertising for genetic testing and medical imaging—other industries with which physicians often have ties.[39-41]

The ethical implications of DTC advertising are complex.[42] On one hand, advertising may promote autonomy, well-being, and distributive justice by informing and empowering patients, improving quality of care, and promoting responsiveness to patients' needs and values.[43-45] This is most likely when the advertisement is not itself disguised in educational programming or celebrity interviews,[46] when the product being advertised has clear indications, and when a physician without industry relationships is available to advise the patient and correct any misunderstandings. On the other hand, advertising may also lead to confusion and even disruption of the physician–patient relationship.[47,48] The very statement, "Ask your doctor about X" implies that one's doctor requires a prompt to provide necessary information, potentially jeopardizing patients' trust in their physicians. As noted above, DTC advertising has direct costs, and it can also increase the costs of the health care encounter or cause harm by distracting from other, more appropriate subjects for discussion.

Although there is some evidence that DTC advertising may improve patient education and physician–patient communication necessary for truly shared decision making—and it might even help mitigate health disparities by encouraging patients of low socioeconomic status to seek care—the primary goal of advertising is to increase utilization.[49,50] One study found a 1% increase in prescription drug spending for every 10% increase in DTC advertising.[51] In some circumstances, this increased use may be appropriate, such as that observed in one study of the effect of aromatase inhibitor advertisements.[52] Nevertheless, to avoid the possibility that advertising might compromise health care quality by leading to overuse or misuse (rather than correction of underuse), the physician's role as an unbiased intermediary and counselor is critical.[53] Unfortunately, the proliferation of ties between physicians and industry discussed above can compromise physicians' ability to play this important role.[54] DTC advertising is particularly problematic when coupled with the absence of an unconflicted provider to help in its interpretation.

As detailed in other sections of this manuscript, industry relationships that can affect the ability of physicians to serve as unbiased intermediaries are broad in range and scope. Recent regulations to mandate disclosure have stemmed from the recognition that industry was increasingly offering physicians not only samples, gifts, dinners, and junkets, but also consulting fees, honoraria for speaking engagements and speakers' bureau membership, ghostwriting services, and substantial financial support for research.[55,56] Although the bias that results from this entanglement with industry may be unintentional and unconscious, and most physicians firmly believe that they themselves cannot be influenced in this way, considerable evidence suggests that such ties do indeed have an effect.[57] Thus, although ethical concerns about the potential effect of these relationships exist even outside the context of concerns related to DTC advertising, they take on heightened importance in this light.[58]

Unfortunately, disclosure such as that mandated in the Sunshine Act is far from a panacea in this context. Patients need physicians' guidance not only because they lack relevant expertise to process complex medical information but also because they are in an inherently vulnerable position when making decisions about their own health. Patients may also find their decision-making abilities compromised by the symptoms of a serious disease such as cancer. Scholars have questioned whether disclosure is a useful approach in general, and the challenges appear particularly acute when considering how best to manage conflicts of interest stemming from physician–industry relationships.[59] It is quite unclear whether patients can truly make appropriate sense of information on physicians' financial incentives or detailed disclosure statements to determine the weight to give their advice in various scenarios.[60-62] Similarly, although one could mandate disclosure of industry spending on DTC advertising and other promotional activities, it is unclear whether such disclosure could serve as a meaningful check on this activity in the way that unbiased physician participation might. Although there are many opportunities for synergy between industry and physicians, there are also many inherent challenges that disclosure alone may be insufficient to mitigate.

PERSPECTIVES FROM INDUSTRY

Collaboration and partnerships between pharmaceutical companies and health care professionals/health care organizations continue to be essential for the development of new and life-saving treatments and medical innovations. Without the engagement of medical researchers and practicing physicians, for example, clinical research on new medicines would be impossible. However, some of these partnerships have raised concerns regarding potential conflicts of interest where a physician's professional judgments or actions regarding a patient may be unduly influenced by relationships with industry. As a result, greater and more detailed transparency into these relationships has evolved over the past decade.

Developing new treatments is the cornerstone of the pharmaceutical industry. On average, nearly 20% of pharmaceutical companies' revenue is returned to conduct research and development that leads to new discoveries.[63] The costs of administrating complex clinical trials typically require high levels of funding that are paid by industry. Physicians are engaged not only to recruit, enroll, treat, and monitor patients but also to design research protocols to scientifically demonstrate effectiveness and/or superiority, promote well-being in patients, and provide clues to the cost-effectiveness of particular treatments and regimens.

Making the research space transparent is particularly challenging because the majority of the payments made or attributed to physicians and teaching hospitals are for reimbursement of out-of-pocket costs associated with treating clinical trial subjects and not for fees or compensation earned by the physician or institution for their own work. In addition, the Open Payments regulations require reporting of "indirect" payments, such that physicians who may not have a direct relationship with any particular pharmaceutical company are still being reported as having received something of value. These complexities, combined with the lack of context, can paint a false picture for the layperson.

Indirect Payments and the Knowledge Standard

Indirect payments are payments or TOVs that are provided to a third-party, noncovered recipient (i.e., not a physician or teaching hospital) and then passed through to a covered recipient. Examples of third-party arrangements that might involve a pass-through to a covered recipient include, but are not limited to, consulting firm services (e.g., McKinsey, BCG), and contract research organizations (CROs) arrangements (e.g., Quintiles, Parexel). When engagement of a third party for services by its nature or by virtue of the contractual terms contemplates or requires the use of a covered recipient to perform the work, the applicable manufacturer (AM; e.g., pharmaceutical, medical device company, or group purchasing organization) will likely need to track, attribute, and report some portion of those payments as indirect payments to a covered recipient. Because physician engagement is essential in many research activities, the indirect payment provision's effect on the research space is significant. As a result of this provision, many CROs have created transparency divisions with the sole purpose of providing data to AMs on the breakdown of the (indirect) payments provided for research.

Steak Eaters, Stakeholders, and Principal Investigators

CMS established $10/$100 (adjusted annually by the Center for Program Integrity) as a de minimis of value transfer to trigger reporting: small TOVs less than $10 do not need to be reported except when the total annual value provided to a covered recipient exceeds $100. The de minimis rule results in the attribution of hundreds of thousands of transactions to just as many physicians. The de minimis threshold is usually not relevant for research, as costs for conducting clinical trials and their corresponding payments are usually well above the limit.

For research, payments are often made to third-party organizations who then use the funds to conduct clinical trials. In an effort to maximize research spend, most research-based pharmaceutical companies look to third parties such as CROs to conduct research associated with their products. By working with multiple AMs, CROs achieve a level of efficiency that any one AM would not be able to on its own. Although it achieves efficiency, engaging a third party inherently results in indirect payments between manufacturers and the (covered) recipient of the funds. Furthermore, the payments made by manufacturers, although based on detailed line-item budgets, usually consist of reimbursements and costs other than salaries or other fees paid to or received

by (covered) recipient principal investigators. As such, amounts being attributed to principal investigators in connection with research can appear very high in total value transfer (especially across multiple companies) but be misleading about actual value received and provide no relevant information about influence. This disconnect is especially egregious in the oncology research space, where patient care, concomitant therapies, required diagnostic equipment, etc., is that much more costly.

Assumptions, Interpretations, and Lack of Context

Because AMs are left to make individual interpretations and assumptions about Open Payments reporting, the data being reported are not amenable to apples-to-apples comparisons. For example, some AMs may report payment activity at the level of the study principal investigator and stop there if no physician is in that position. Others may go further to attribute funds to site principal investigators, while others may go still further to attribute funds to all physicians (including sub-investigators) actually working with patients. Each approach provides a different view of the same payment data. However, without knowledge of the underlying assumptions made, third parties could reach different and sometimes incorrect conclusions. Context to the public about the potential differences in application and interpretation of Open Payments is still needed.

Effect on Clinical Oncology Practice

As our understanding of oncology deepens to reveal that what was once believed to be a single disease (or a collection of diseases differentiated on where a tumor primarily presents) is, in fact, more than 200 disparate diseases whose nature depends more on an individual patient's specific molecular constitution than where the primary tumor first presented in that patient clinically, we will need to design and implement smaller, smarter, more nimble clinical trials to develop the suite of tailored medicines (and combinations thereof) that have the greatest potential to treat an individual patient's unique disease. This democratization of clinical trial design is likely to require an even greater absolute number of these smarter, nimbler trials, requiring industry to have even more relationships, with attendant financial ties, to individual physician investigators who either design and sponsor the trials themselves or partner with industry to manage and implement this important clinical trial work.

At the same time, the parallel global trend of increased transparency threatens to cast a pall over this necessary work, as some—concerned by a recent history replete with highly publicized allegations of industry marketing abuses—question the legitimacy of industry's continued financial ties with physicians who stand in the position to prescribe their medicines. Certain physicians, or their institutions, might react (or already have) by curtailing their ties to industry-sponsored research and development work, just when the pursuit of good science requires more partnership. We, as a society, need policies and practices that foster better collaboration across industry, private practice, academia, and government to pursue this good science for society's benefit. Meanwhile, and for some time to come, the burden will likely be placed on industry and physicians to explain how these legitimate relationships foster the greater societal good in an effort to win back our skeptics' trust.

CONCLUSION

Oncology research and practice in the modern era require collaborations between academic physicians and industry. These collaborations provide challenges and opportunities that the entire oncology community must understand and address—especially the complexities that result from these relationships. These relationships which are necessary to continue advancing the field of oncology influence decisions from the level of the individual patient and provider, academic institutions, professional societies, and, most recently, national health policy. As we strive to provide the best and most promising therapies to our patients, we must acknowledge the issues surrounding relationships with industry and learn to navigate and overcome these challenges.

Disclosures of Potential Conflicts of Interest

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HEALTH SERVICES RESEARCH AND QUALITY OF CARE

Quality Measurement in Health Care: Tools to Improve Care

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Cancer Care Quality: Current State and Future Directions

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OVERVIEW

Delivery of high-quality medicine is essential in all fields, but it is particularly crucial in cancer medicine in which therapies can be toxic and life-threatening and appropriate treatment can lead to long-term remissions or cure, and when poor therapy compromises survival. Variability in postoperative mortality has been demonstrated for several complex cancer surgeries, depending on surgical expertise and volumes. Systemic therapy, including both cytotoxic and targeted therapies (which are the backbones of many curative regimens), can have severe toxicities. Small upward errors in dosing or schedule can result in unnecessary morbidity and mortality, and they can result in reduced efficacy and poor outcomes. Similarly, radiation therapy is a critical modality in the treatment of so many cancers, but clinically important morbidity and mortality can be associated with it. Methods to continually assess quality in ways that lead to interventions to improve care are essential in cancer medicine today, and they can be viewed as an obligation of our profession.

Quality of any medical care is important, but it is particularly important in cancer care. Quality can be viewed through different lenses, including safety of practice, adherence to treatment guidelines (process measures), and outcomes that include overall survival, cancer-related survival, and quality of life. It is important to consider each of these quality metrics.

SAFETY

In the 1990s, there was a great deal of focus on patient safety. An Institute of Medicine report, "To Err is Human: Building a Safer Health System," published in 1999, examined medical safety and vulnerabilities that can lead to patient harm.[1] A critical component of this process was the acknowledgment that humans, in this case even medical personnel with appropriate training such as physicians, nurses, and other key health care personnel, can make errors that could lead to patient harm or death.

Cancer care is complex and multidisciplinary. A patient with locally advanced rectal cancer may receive concurrent chemotherapy and radiation that might be followed by a surgical resection, the safety of which can be influenced by the toxicity from preoperative therapy. A medical oncologist would prescribe the chemotherapy, including agents, dosing (e.g., based on body-surface area calculations relying on accurate measurements of height and weight), and schedules; a pharmacist would prepare the therapies; and an oncology nurse would administer the drugs. At the same time, a radiation oncologist—together with physicists, dosimetrists, and others—would plan the radiation ports and daily and total doses. The large number of individuals involved and the complexities of the therapies and calculations needed for correct dosing present a significant challenge in assuring care is administered as planned. In addition, care is likely to bridge out-patient and in-patient settings and sometimes involve several institutions. One calculation or human error in this process could lead to higher dosing than planned and added toxicity or death. Likewise, an error resulting in lower than planned dosing could reduce the likelihood of tumor control and long-term remission or cure.

Many errors go unnoticed or are only discovered later when it becomes clear that the outcomes were suboptimal. Continual assessment of processes and the identification of errors that occur in some part of the process, but are identified before reaching the patient and are corrected (near misses), is essential for any program. It is only with continual vigilance that safety will be at its highest level. Assuming that systems are safe can only lead to increased errors over time. The American Society of Clinical Oncology (ASCO) and the Oncology Nursing Society (ONS) have published guidelines for safe oncology practice.[2] Adherence to these guidelines is a component of their Quality Oncology Practice Initiative (QOPI) certification process, which is described later in this article.[3]

Health information technology can be used to improve safety in oncology practices, particularly through the use of electronic health records (EHRs) and computerized chemotherapy order entry systems.[4] These systems do not eliminate the need for human intervention; therefore, there can continue to be human error, so continued vigilance is necessary.

A culture of safety is key to reducing errors to their lowest possible level, with the understanding that errors probably

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will never be eliminated altogether. All members of a team must be free and willing to speak up when something seems wrong, and each team member must respect and encourage this approach. Hierarchical systems in which some team members are viewed as subservient add considerably to system vulnerabilities. An organizational structure that continually assesses culture and processes, with clear leadership and accountability, is essential in any cancer practice.

However, as important as safety is, it does not consider quality of cancer care in regard to appropriateness of treatment that is designed to provide optimal patient outcomes. It is possible for a medical oncologist to order a regimen correctly, to have it prepared and administered as intended with optimal safety, but if it is not the ideal regimen for the patient's particular type of cancer, the patient outcome is likely to be less than it might be.

PROCESS QUALITY

Much of current cancer care quality measurement is focused on process measures. Based on a high level of evidence from randomized clinical trials, a patient with stage III colon cancer should receive adjuvant chemotherapy. Most quality programs, however, only determine if the patient received chemotherapy. They do not assess whether the patient received the right chemotherapy, whether it was given in appropriate doses and schedule, and they do not assess patient toxicity, quality of life, or survival. There is an implication that if the patient received chemotherapy in this circumstance, appropriate therapy was given, and, by inference, outcomes would be ideal. These are big assumptions. Additionally, much of what oncology providers deal with on a day-to-day basis involves decisions where no high-level evidence exists, which narrows the number of important clinical decisions that can be assessed for quality.

Process measures are used for many reasons. They can be defined, measured, and assessed on recently treated patients. There is an assumption that receiving the right therapy will result in optimal ultimate outcomes. This assumption, however, can be variably defined. Did the patient with stage III colon cancer receive chemotherapy? Do we know what chemotherapy he or she received? Do we know if dosing and schedule was appropriate? Do we know if toxicities were managed appropriately? Care processes can be evaluated on a small random sample of patients or on all patients meeting defined criteria. ASCO's QOPI assesses a random subset of patients with a particular diagnosis and stage for appropriate therapy. For example, patients who have stage III colon cancer should receive adjuvant chemotherapy.[3] The Commission on Cancer (CoC) uses the National Cancer Data Base (NCDB), which will be described in more detail later in this article, to assess all patients treated at a CoC-accredited hospital for this same metric.[5] Process measures are most useful for a practice or hospital when data from other practices and hospitals are available to compare performance. This is true for both the QOPI program and the CoC quality program. In neither case, though, are the specific chemotherapeutic agents assessed, nor are the appropriateness of dosing and schedule.

Process measures can assess the current state of practice for a particular physician group or hospital. They also can be used as a quality improvement tool if performance is suboptimal. The QOPI program examined chemotherapy given during the last 2 weeks of life as a quality metric for end-of-life care. A group in Michigan realized that its rates of utilization of chemotherapy during the last 2 weeks of life were much higher than other QOPI programs. The group then designed interventions to influence practice and their performance quickly improved substantially.[6]

Some process measures derived from very high-level evidence represent relatively low bars to which excel. Both QOPI and CoC examine hormone therapy rates for women with certain stage, hormone receptor–positive breast cancer. Most programs rate very high on this metric. As such, most programs have little room for improvement and the measure does not represent a good approach to comparing performance across programs.

OUTCOMES MEASURES

Patient outcomes, such as overall survival, which takes into account survival from the cancer as well as potential complications of therapy, might be the ultimate quality metric. Survival as a quality metric, however, presents many challenges.

Survival depends not only on the stage of disease, but also on a number of related and unrelated factors. Gender and age have profound effects on survival, and these data are always available in databases for stratification. Socioeconomic status, ethnicity, performance status at presentation, comorbidities, and distance from the patient's home to his or her treating center all affect survival rates, but not all of these factors may be

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KEY POINTS

- Cancer care providers have an obligation to measure the quality of their treatment to be certain they understand its current state and can design interventions to continually improve performance and patient outcomes.
- Cancer care quality encompasses the safety of care delivered, process measures assessing whether appropriate treatments were administered, and outcome measures that include survival and quality of life.
- Cancer care is complex, provided by medical, radiation, and surgical oncologists, and oncology nurses, with key support from pathologists and radiologists, and spans in-patient and out-patient venues, which makes quality assessment and improvement challenging.
- The Commission on Cancer's Quality program using the National Cancer Data Base and the American Society of Clinical Oncology's Quality Oncology Practice Initiative are examples of broad-based national quality programs.
- The use of health information technology will play a key role in future measurement of cancer care quality.

available for analysis. Comorbidities, in particular, are often complex, hard to quantitate, and variably documented in records. In addition, biologic factors influence survival. A prime example is HPV status in patients with head and neck cancer, in which HPV status radically affects survival with the same therapies.[7] If survival is not stratified for these factors, data will be difficult to interpret or could be misleading.

For many cancers, such as early-stage breast or colon cancer, survival is best assessed at 5 or 10 years after diagnosis. This is because it takes that long for a substantial number of recurrences to occur and for those recurrences to lead to death. Therefore, because of the delay in data entry into registries, survival is reflective of treatment administered 6 or more years earlier. Quality of care from 6 years ago will not necessarily be indicative of more recent efforts to improve quality. In addition, it reflects treatments chosen 6 years before and it does not take into account improved treatments introduced in the interval. Physicians and other providers frequently complain about these factors, suggesting the data are no longer relevant.

In some circumstances, treatment influences survival very little. Most patients with pancreatic cancer present with advanced disease, and current therapies, although marginally better than previous therapies, have very little influence on survival. Therefore, differences in the quality of care may not translate into differences in survival.[8]

In other circumstances, treatment may be so standard and reasonably easily administered that differences in care at one institution vs. another may not be great and will not translate into differences in survival. Examples might include the administration of hormone therapy for patients with estrogen receptor–positive breast cancer, or the administration of chemotherapy for patients with stage III colon cancer.

Quality of life is another important outcome. Optimal management of complex therapies, including surgery, radiation, and systemic therapies, is essential to reduce short- and long-term toxicities. Radiation therapy delivered for the treatment of head and neck cancer is complex and carefully constructed intensity modulated radiation therapy can minimize short- and long-term complications. Less sophisticated approaches result in greater speech, swallowing, and mobility problems both short and long term.[9] Degrees of expertise in performing prostatectomy can influence rates of impotence and urinary incontinence.[10]

Historically, health care providers have recorded toxicities and quality of life inconsistently and data are not always available to truly answer quality-of-life questions. Patient-reported outcomes are becoming increasingly important in documenting quality of life, toxicity specifics, and other important clinical outcomes. Patient-reported outcomes can be electronically recorded by the patient and entered into databases, either clinical databases such as electronic health records, or research databases.

QUALITY MEASURE DEVELOPMENT

The development of quality measures is an important first step in quality assessment and improvement. Quality mea-

sures should explore aspects of care that are important for patient outcomes. They should be based on solid medical evidence and targeted toward aspects of practice in which there is room for improvement. Quality measures must be defined so that the necessary data elements can be extracted from available databases.

DATA SOURCES AND CANCER CARE QUALITY

Ideally, quality of cancer care can be assessed in ways that tax human capital as little as possible. Manual abstraction of patient charts or other documentation can demand considerable time from clinical staff that might be better spent on activities more directly related to clinical care. Electronic data abstraction from EHRs or other databases can measure many aspects of clinical care more efficiently, including those related to quality of care. Not only is this method less demanding on people's time, but it also allows a practice to assess all of its patients with a particular disease and stage, or those who are receiving a particular treatment, whereas manual chart abstraction often limits the number of patient charts that can be reviewed.

Electronic health records provide some advantages as data sources for quality work. Information is entered "live-time" during the provision of care and becomes available for assessment almost immediately. There are several disadvantages, however. Frequently, important data are contained in text notes, or as other nonstructured data, which cannot easily be extracted in usable ways. Although natural language processing can often extract information in a meaningful way, it may have variable accuracy and completeness. Certain information, such as cancer staging, can be entered into an EHR as structured data, but it requires providers to enter the data and to enter it correctly. Data may not be entered at all, and, if entered, it may be entered incorrectly. Accurate diagnostic and staging information in cancer care is critical for almost any other metric to be assessed. Electronic health records frequently contain complete laboratory data and treatment specifics (e.g., drugs, doses, and schedules). For a patient with stage II estrogen receptor–negative, HER2–negative breast cancer who is receiving four cycles of doxorubicin and cyclophosphamide as adjuvant therapy, an EHR should be able to provide the drugs, doses, and whether there were dose reductions, or changes in the schedule; and hematologic values to assess that aspect of tolerance. But knowing that this was the appropriate therapy depends on having accurate anatomic and nonanatomic staging data. If the stage, estrogen receptor, or HER2 status was not entered, or entered incorrectly, there is no way of knowing if this is the appropriate therapy. EHRs are refined continually for usability, decision support, and conversion of data from free text to structured data with these issues in mind.

Registry data also have advantages and disadvantages. Most often, certified tumor registrars trained in the abstraction of data and entry into registry systems enter the data. Registries usually have data on all patients with cancer who are receiving some of their treatment at the facility. Staging

data can be very accurate and other aspects of care and follow-up well delineated in structured data fields. Data often are entered with some lag time—sometimes 6 to 12 months after the event. Although anatomic staging may be complete and accurate, nonanatomic staging, particularly biomarkers, are not always recorded. Estrogen receptor and HER2 data are routinely collected for breast cancers, but newer markers such as *KRAS, BRAF,* or *EGFR* kinase mutations frequently are not. These factors are becoming increasingly important for their prognostic value and for determining correct therapy choices. In addition, entries may indicate that systemic therapy was administered, yet the specifics of that therapy often are not given. It may be known that the patient received chemotherapy but not which chemotherapy. Also, when systemic therapy or radiation therapy is administered at practices outside of the registry's hospital, data are not always available to enter into the registry. Comparing data in registries against claims data has demonstrated this point.[11]

Currently, databases such as registries and EHRs do not communicate well, requiring dual entry of data that is costly and increases risk of data entry errors. Efforts are underway to better link EHRs and registries to overcome some of these challenges, increasing both accuracy and reducing workload.

ASCO'S QUALITY ONCOLOGY PRACTICE INITIATIVE
A decade ago, ASCO undertook an experiment to define quality measures in oncology practices and invited practices to voluntarily participate.[3] Initially, there was little incentive to participate, but many practices chose to do so. In the following years, many quality measures were added to the QOPI slate and more practices chose to participate. Quality was assessed by manual chart abstraction on a subset of patients with a particular disease, stage, or situation. Practice compliance with the measure was assessed and compared to other QOPI practices. Later, a certification program was introduced that involved a site visit that not only assessed compliance with quality measures but also adherence to ASCO/ONS safety standards.

Practices voluntarily participated, largely because they thought it was the right thing to do. In some circumstances, however, additional benefit was established, as in the case of a partnership between Blue Cross Blue Shield (BCBS) of Michigan and the Michigan Oncology Quality Consortium.[12] Practices were able to show substantial improvement in quality metrics and financial rewards for participating were established between the practices and Blue Cross Blue Shield.

The major disadvantage of the QOPI program is its reliance on manual chart abstraction of a small sample of patients. Work is underway to transition QOPI to an electronic abstraction process (eQOPI), which would be a major advance and benefit.

THE COMMISSION ON CANCER QUALITY PROGRAM
The CoC is an arm of the American College of Surgeons that accredits hospital cancer programs.[13] Currently, more than

1,500 hospitals in the United States are accredited. Accredited hospitals transfer their registry data into a de-identified database, the NCDB, which is cosupported by CoC and the American Cancer Society. Accredited hospitals can enter a portal to view their performance against many quality measures and compare them with other CoC-accredited hospitals. In addition, an annual report is produced for each accredited hospital—The Cancer Quality Improvement Program (CQIP). The CQIP contains the hospital's performance for 12 quality measures (in the 2014 report), 30- and 90-day postoperative mortality for six complex cancer surgeries (thoracotomy, esophagectomy, cystectomy, gastrectomy, rectal cancer resection, and pancreatectomy), and survival data for several more common cancers.

A major advantage of the NCDB quality program is that manual chart abstraction is not necessary. Quality data are derived electronically from the database for all patients who have cancer with a particular diagnosis and stage. It should be noted, however, that the NCDB is registry-derived data and registry data are manually entered by registrars. An individual hospital's data can be compared against all other CoC-accredited hospitals, or just hospitals in their region, or hospitals of similar type (e.g., community vs. academic cancer center). Disadvantages include registry data that are often 1 to 2 years old before completely entered into the database. Furthermore, not all desired data are housed in the NCDB. Programs such as the CoC's Rapid Quality Reporting System are driving more timely entry of registry data to affect quality of ongoing care."[13] Specifically, there is little granular data on specific systemic therapies administered and disease-free survival and cancer-related mortality data often are not there. Measures must be designed around what data are available in the NCDB.

COST OF DOING CANCER CARE QUALITY
A hospital or practice that addresses quality measures seriously has a team of individuals undertaking this work. This group often includes physicians, nurses, and individuals who manage the databases, data extraction, and analyses. Participation in the quality programs described above also carry a cost. The exact costs of doing cancer-quality work likely vary greatly among institutions and practices depending on size, databases available to be queried, and other factors. Currently, with few exceptions, practices and hospitals do not gain financially by participating in quality programs in a degree sufficient to offset these costs. In the future, reimbursement for clinical services hopefully will be more closely linked to performance and quality.

FUTURE DIRECTIONS
Our profession has an obligation to measure the quality of our work and to continually strive to improve our practice. This will become even more important as new biomarkers and therapies become available in cancer care and treatment

becomes increasingly multidisciplinary and complex. This can only be achieved when structured quality programs are in place. Funding those programs is not trivial, particularly in the current health care financial climate. Hopefully, in the future, reimbursement will be tied to quality of practice and outcomes for patients.

Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

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LEUKEMIA, MYELODYSPLASIA, AND TRANSPLANTATION

Acute Lymphoblastic Leukemia: A New Era of Targeted and Immunologic Therapies

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The Challenges of Managing Older Patients with Acute Lymphoblastic Leukemia

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OVERVIEW

Acute lymphoblastic leukemia (ALL), predominantly a disease of children, has a second incidence peak in older adults. Patients older than age 50 but younger than age 65 may be included in trials of intensive treatment with curative intent, but their outcome is poor with high nonrelapse mortality (NRM), high relapse rates, and low overall survival. Using limited published data from the United Kingdom ALL XII and HOVON trials, this manuscript explores the reasons for the high transplant-related mortality (TRM) and presents early data from the United Kingdom ALL 60+ and United Kingdom ALL XIV studies. Factors affecting therapeutic decisions for older patients are discussed. A case study illustrates some of the issues involved in managing these patients and the need to individualize therapy and consider all options. There may be a role for reduced intensity allografting in selected, fitter patients older than age 50; this article presents preliminary transplant data from United Kingdom ALL XIV that prospectively assesses this therapeutic modality. Detailed discussion of tyrosine kinase inhibitors and the potential place of novel targeted antibodies and immune T-cell therapies will be not discussed in detail. Finally, there is a description of the major outstanding issues and the trials that are needed to inform decision making and improve outcome in this challenging group of patients.

This article will focus on patients with ALL older than age 50 who are known to have a poor outcome in terms of complete remission (CR) rates and long-term survival (Tables 1 and 2, Fig. 1).[1] However, different investigators have used various age limits in defining older patients with ALL. Outcome worsens markedly when patients are older than age 40 and is considerably worse in patients older than age 60. Furthermore, Surveillance, Epidemiology, and End Results (SEER) Program data from the United States show that, unlike every other age group, there has been no significant improvement in outcomes during the last 25 years. In 1984, 8.4 ($\pm$ 3.4%) of patients older than 60 survived compared with 12.7 ($\pm$ 2.9%) from 2000 to 2004, a nonsignificant increase of 4.3%.[2]

In adults, the median age at diagnosis is older than age 60, making effective therapy of the older patient an important area of unmet need.[3-6] The age-specific annual incidence in individuals older than age 60 is 0.9 to 1.6 per 100,000 compared with 0.4 to 0.6 per 100,000 in the 25-year to 50-year age group. The number of cases of ALL occurring in older patients will increase as the general population ages.

DIFFERENT BIOLOGY OF DISEASE AND DIFFERENT PATIENT BIOLOGY
Disease Biology

Compared with younger patients with ALL, older patients have a reduced male to female ratio, their disease is more likely of B-cell origin, and there is greater coexpression of myeloid antigens; these factors portend a worse prognosis, although more recent studies suggest myeloid antigen expression may have minimal prognostic value. Cytogenetic findings such as Philadelphia chromosome positivity, t(4;11), complex cytogenetic abnormalities (more than five chromosomal changes), and low hypodiploidy/near triploidy result in inferior survival rates.[7] These changes are all more common in older adults. Good prognosis lesions, such as high hyperdiploidy, t(12;21), and a normal karyotype, are less common in older patients. The incidence of Philadelphia positivity was felt to progressively increase with age, but this has been challenged by Moorman's population-based study,[8] which indicates a plateau past the age of 50.

THERAPEUTIC DIFFERENCES

Available agents for remission induction therapy include steroids, vincristine, doxorubicin, and various formulations of asparaginase. Choosing the right agents for each patient should take into account reduced renal function, a tendency to more mucositis, and a higher probability of confusion with steroids, infection, and metabolic derangement. Steroids are also more likely to result in symptomatic myopathy and, undoubtedly, contribute to infection. Drug interactions are also more likely in this age group. Concomitant medications

TABLE 1. Prospective Studies of Acute Lymphoblastic Leukemia in Patients Older Than Age 54

Author	Complete Remission Rate (%)	Median Survival (Months)
Kantarjian 1994	65	11
Bassan 1996	59	9
Delannaoy 1997	85	14
Delannaoy 2002	58	9
Offidiani 2003	73	Not stated

should be stopped, if possible. Nutrition is a major issue; all older patients should be seen by a dietitian and their diets proactively managed.

One of the key treatment decisions in this age group is whether an older patient can safely receive conventional doses of anthracycline. A baseline echocardiogram with estimation of ejection fraction is essential. However, many patients will have had a past history of ischemic heart disease or abnormal echocardiograms. Cardiac arrhythmias are common pretreatment (and during induction) and may require cardiac consultation and a change in therapeutic strategy. Li-

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KEY POINTS

- Older patients with ALL require an individualized assessment of comorbidities and therapy adapted to their performance status, disease response, and personal treatment goals. Newer targeted therapies are likely to play a larger role.
- Optimal postremission therapies in older patients are unknown as are their effects on quality of life and in maintaining complete remission (CR). Reduced intensity conditioning (RIC) allografting in fit patients who have responded well to therapy and have high-quality donors deserves further exploration.
- Arguably, older patients with Philadelphia-positive (Ph-pos) ALL have better outcomes than older patients with Ph-negative disease. This patient group can reliably achieve CR with vincristine, steroids, and a tyrosine kinase inhibitor (TKI) with minimal toxicity. Medium-term survival can be achieved in many older patients with gentle maintenance therapy and a TKI. Using a different agent at relapse may prolong survival.
- Internationally, ALL investigators need to target this neglected group of patients by opening clinical trials that ask questions aimed at improving survival and the quality of that survival. Physicians who manage these patients are urged to enter patients into these clinical trials so that we can learn which therapy can be tolerated and is most efficacious. These basic studies would provide the background data that will enable study of newer targeted therapies that have less marrow and extramedullary toxicity.

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posomal daunorubicin deserves further testing and liposomal vincristine may result in less autonomic neuropathy.

GOALS OF THERAPY AND PHILOSOPHY OF TREATMENT

Progress in ALL in older patients has been inhibited by a lack of systematic prospective trials and a lack of consensus about the goals of therapy. Only a small percentage of older patients are enrolled in trials,[5] and these patients may not represent the entire group. Prospective studies of older patients show CR rates that range from 30% to greater than 70%, but median survivals generally less than a year. Some studies using a less aggressive treatment intent showed similar survival. Their data may be informing us that one treatment does not fit all: that some are suitable for treatment with curative intent but many are not.

Intensive, prolonged inpatient chemotherapy, with high toxicity and a substantial NRM, can only be justified in this age group within the context of a clinical trial or if there is a significant chance of at least medium term survival.

HOVON

The fairly small-scale data by the HOVON group highlights the uncertainties of how to manage this disease.[9] In 24 patients age 61 to 70 (who were undoubtedly highly selected), 79% achieved CR, and overall survival at 3 years was a remarkable 50%. However, the price for these results was 21% induction mortality. Patients and physicians might accept this NRM as it was accompanied by a realistic chance of medium-term survival. Three of the 24 patients underwent an allogeneic transplant.

POTENTIAL ROLE OF MINIMUM RESIDUAL DISEASE

Eligibility for the United Kingdom ALL XIV trial is for people age 65 or younger, although patients older than age 60 who are less fit may be entered onto the United Kingdom elderly patient trial (ALL 60+). There are few prospective minimum residual disease (MRD) data in the age 60 or older group.

Of the 19 patients older than age 60 analyzed so far, only three were MRD negative after phase I, but five of 16 were negative after phase II (Zakout, unpublished data) with some additional patients being very low-level positive. This shows that intensively treated older patients can be rendered MRD negative. How to use this very limited information is uncertain. MRD-positive patients, depending on their clinical well-being, could be informed of the result and given the choice of therapy to attempt to render them MRD negative or to receive more gentle palliative treatment.

Patients who are MRD-negative, on the other hand, would be candidates for RIC allografts, further intensive chemotherapy, or possibly even an autograft. We need further MRD

TABLE 2. Outcome Data Concerning Older Patients with Acute Lymphoblastic Leukemia

Group/Study	Age	No. of Patients	CR Rate (%)	OS (at 3 to 8 Yrs)	Author
UK NCRI	55-64	100	70	19% at 8 yrs	Sive 2012
CALGB	> 60	129	57	12% at 3 yrs	Larson 2005
MD Anderson	> 60	44	79	17% at 5 yrs	Kantarjian 2000
SWOG 8419	50-84	85	41	Not reported	Petersdorf 2001
GIMEMA 0208	50-60	121	68	15% at 8 yrs	Annino 2002
PETHEMA ALL96	56-67	33	58	39% at 5 yrs	Sancho 2007
SWOG 9400	50-65	43	63	23% at 5 yrs	Pullarkat 2008
EWALL	56-73	40	85	Not reported	Gokbuget 2008

Abbreviations: CR, complete remission; OS, overall survival; Yrs, years.

data in patients who are less intensively treated. It is likely that some of those patients will also be MRD negative; this gives the option of escalating or de-escalating therapy. Most available MRD data uses molecular techniques; MRD data using flow cytometric techniques require further standardization and prospective evaluation. This latter technology is more frequently used in the United States.

UNITED KINGDOM DATA
Issues with the Data

Fewer patients in this age group are enrolled in trials, and they are clearly a selected group and are probably unrepresentative of newly diagnosed older patients with ALL. The chance of early death is high as is refractoriness to chemotherapy.

SIVE ET AL

The United Kingdom Medical Research Council (MRC)/ Eastern Cooperative Oncology Group (ECOG) collaborative group reported outcomes of therapy in 100 patients older than age 55 out of a total of 1,914 recruited to United Kingdom ALL XII/ECOG2993 (median age 56, range 55 to 65).[10] Patients were treated with the full protocol as detailed in Goldstone et al,[7] with no planned dose reductions. Com-

pared with younger patients on study (younger than age 55), more were female, Ph-pos (28% vs. 17%, p = 0.02) and slightly more were in a high-risk cytogenetic group (46% vs. 35%, p = 0.07). The chance of CR was reduced by 20% (73% vs. 93%, p < 0.001).

Strikingly, 5-year overall survival was 21% in the older group compared with 41% in the younger group (Fig. 2). Induction mortality was higher (18% vs. 4%) and infections were more frequent (81% vs. 70%, p = 0.05). A reported infection was associated with higher mortality, particularly if it occurred in both phases of induction. Bacterial infections also occurred at a 50% greater frequency in the older age group. Forty-six percent of older patients had dose reductions compared with 28% in the younger group (p = 0.0009). The most common reason for dose attenuations was hepatic derangement and asparaginase was the drug most often omitted. Reductions in chemotherapy dose were not significantly associated with worse outcomes but numbers were small.

Importantly, Sive et al concluded that the induction protocol used in this study was too intensive for many older patients with ALL. They further stated that stratifying patients based on their disease risk and fitness for therapy might be a way of individualizing therapy; those who are less fit should be treated less aggressively. Although unproven, using MRD to guide decision making may also be valuable.

ALL 60+

Recognizing the lack of prospective data to inform decision making, the United Kingdom National Cancer Research Institute ALL group initiated a prospective study in patients with ALL older than age 60 with the goal of informing how physicians and patients use information about comorbidities and performance status at diagnosis to determine therapy. Comorbidity information is being collected using a variety of tools that have been validated in other groups of infirm patients including many with cancer. There is also a noninterventional registration arm (of patients not wishing to participate) that will enable the estimation of the proportion of older patients with ALL willing to enter prospective trials.

FIGURE 1. Survival of Adults with Acute Lymphoblastic Leukemia by Age Group
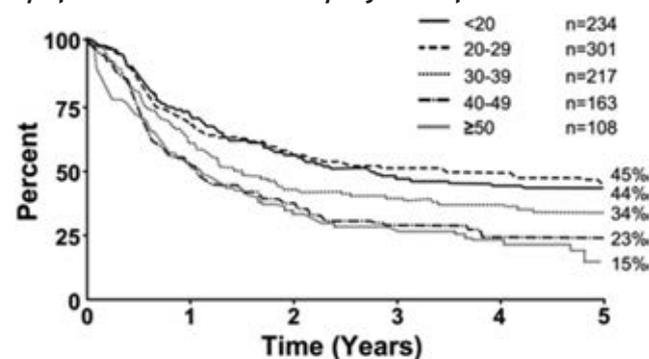
Adapted from Rowe JM et al. *Blood.* 2005;106:3760-3767.

FIGURE 2. Survival of Patients by Age at Entry to Study Showing (A) Overall Survival and (B) Event-Free Survival in All Patients and (C) Overall Survival in Just Those Who Received Chemotherapy
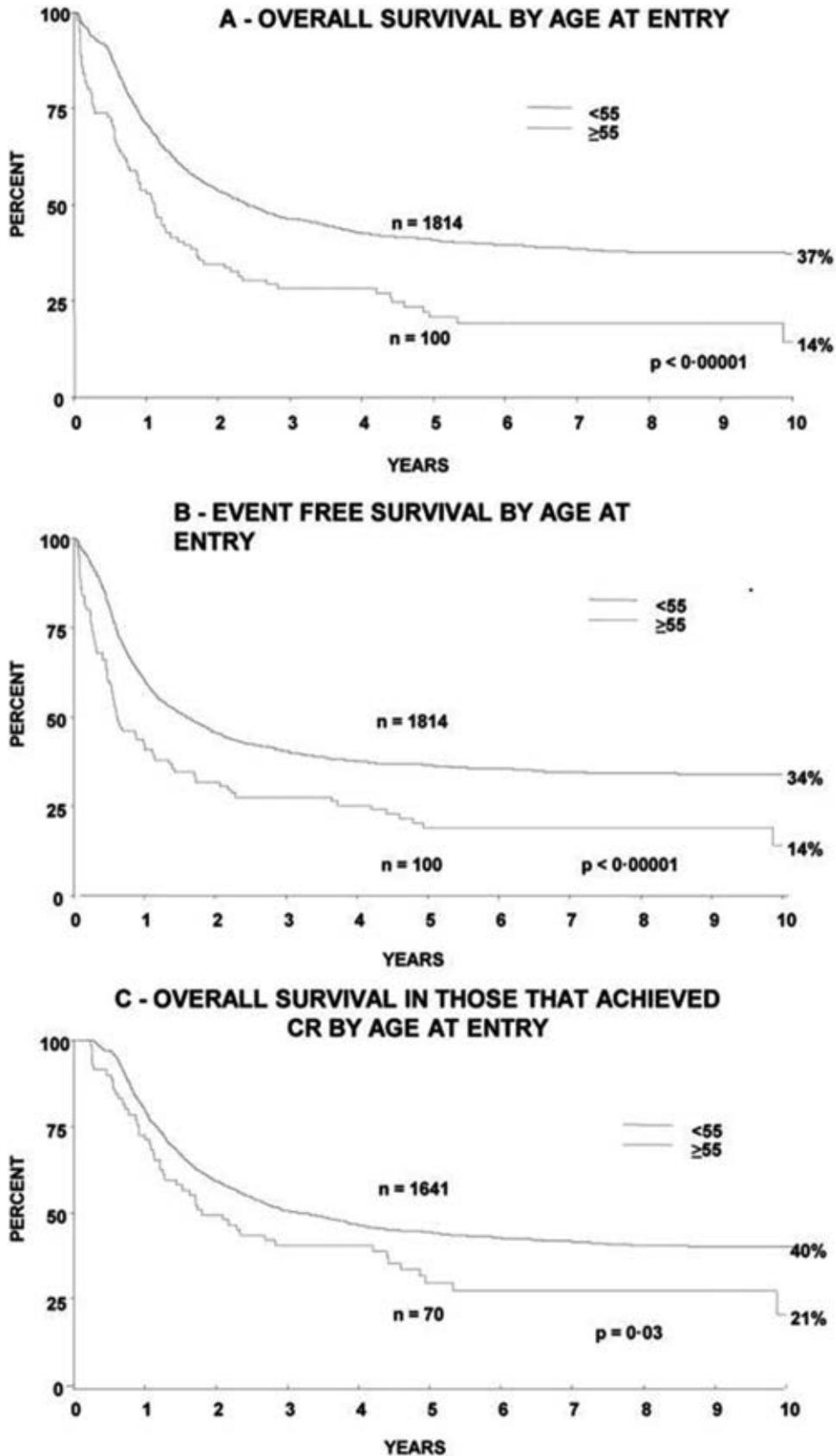
FIGURE 3. Treatment Schema for United Kingdom ALL 60+ Trial Showing Four Treatment Arms and One Registration Arm
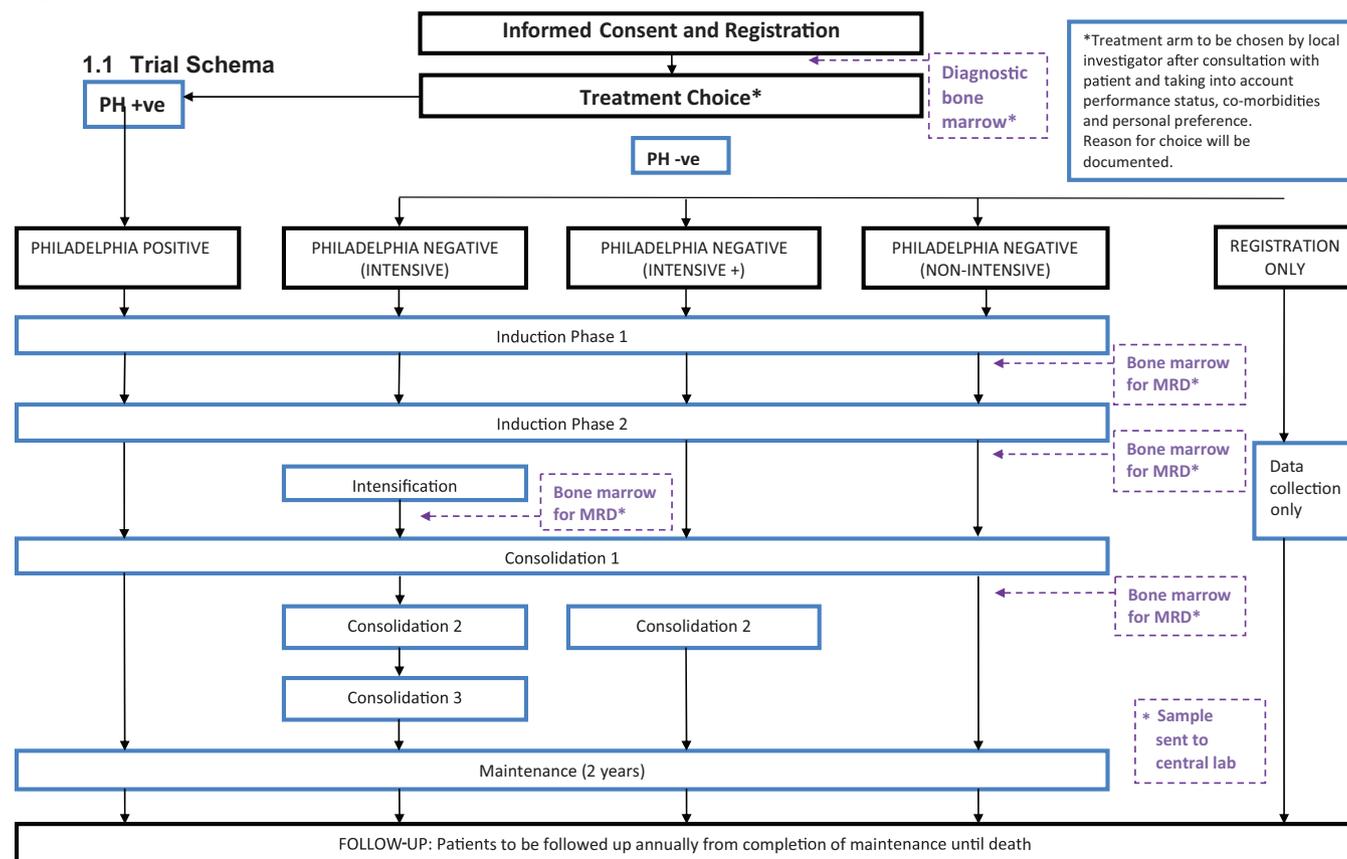
Four treatment arms ranging from very low to high intensity are available to patients enrolled in the study (United Kingdom CRN ID 12988; Fig. 3). The primary endpoints of the study are CR rate after two cycles, event-free survival at 1 year, and treatment-related mortality. Further aims include assessing quality of life (QOL), inpatient stays, and the prognostic value of MRD at three time points. We will further assess tolerability of treatment by assessing certain adverse events.

The trial is accruing slowly, but to date we have preliminary data about 39 patients from 21 centers. The median age of patients is 67 and seven patients are Ph-pos. Twenty one have been assigned to the intensive or very intensive arms. Only 18 patients are currently evaluable for response after phase II. There has been no NRM, and 13 have achieved CR. Two patients have died of ALL. These data will be updated just before the 2015 ASCO Annual Meeting. HOVON and New Zealand are planning to join the study.

During the next 3 years, we will collect data about postremission therapy and its effect on QOL and need for hospitalization. Having analyzed these data, in the next study we will add in some novel agents aiming to improve efficacy without worsening toxicity.

UNITED KINGDOM ALL XIV TRIAL

To date, 394 of 720 planned patients have been recruited to the United Kingdom ALL XIV multicenter study of adults with ALL age 25 to 65. This randomized controlled trial is evaluating up-front rituximab and nelarabine in B-cell and T-cell disease respectively, as well as testing reduced intensity allografting in high-risk patients older than age 40. The protocol was amended after the first 92 patients because of excessive NRM, mostly in older patients. The anthracycline dose was halved (from 60 mg/m^2 to 30 mg/m^2) and doses of PEG-asparaginase reduced from two to one or eliminated in patients with Ph-pos disease.

One-hundred fifty-two patients older than age 50 were entered (139 patients with B-cell disease and 13 patients with T-cell disease, median age 56.5). Philadelphia positivity was seen in 38% of evaluable patients. CR was achieved in 26 of 39 evaluable pre-amendment patients, nine patients died with evidence of leukemia, and four died of NRM (10%). NRM will be analyzed in the patients older than 50 who were enrolled in the study after the protocol amendment. To date, 17 of 137 evaluable patients have relapsed. Forty-four patients older than 50 have proceeded to a RIC allograft (15 sibling donors and 29 unrelated donors). The outcome of all patients

who received RIC allografts will be discussed later in the manuscript.

GERIATRIC ASSESSMENT, RECOMMENDATIONS FOR ADJUSTED THERAPY, USE OF NEW AGENTS

A thorough pretreatment assessment of comorbidities is important. Diabetes and prior malignancy are commonly seen.[5] These objective geriatric assessments have become more formalized recently.[11] On the basis of simple, easy-to-apply criteria (e.g., activities of daily living, performance status, assessment of cognition, and physical function), patients can be divided into three categories: fit, vulnerable, and frail.

Some very simple individualized adjustments to treatment can make treatment effective and tolerable. Shortening the period of neutropenia with granulocyte-colony stimulating factor (G-CSF) is sensible, and one study showed that this resulted in improved survival.[12] Some older patients are unable to tolerate the combination of prolonged neutropenia in the presence of steroids and require omission or dose reductions in myelotoxic drugs. If these drugs are omitted, physicians should consider using rituximab in patients with CD20-positive B-cell disease. Two randomized trials are currently evaluating rituximab's efficacy, but historic control data are encouraging.[13]

Asparaginase is more likely to cause severe hepatic dysfunction especially in the presence of hepatotoxic drugs such as omeprazole, cotrimoxazole, and imatinib. Asparaginase should be used sparingly, if at all, in patients older than 60 and with very careful monitoring.

Patients with significant smoking histories and concomitant cardiac and pulmonary dysfunction tolerate sepsis poorly. Although its use remains controversial, use of quinolone prophylaxis, G-CSF, and very early treatment of possible sepsis is recommended.

The use of agents such as blinatumomab may be an effective means of eliminating MRD with less immune suppression, but large scale efficacy data are lacking in older patients as are tolerability data, especially with regard to central nervous system toxicity.[14] Nelarabine may be an important adjunct up-front in T-cell disease;[15] United Kingdom ALL XIV is examining this issue. Inotuzumab has been examined in a phase III comparison with standard of care therapy in relapsed disease; this trial should yield important safety and efficacy data in patients older than age 50.[16-17]

PH-POS ALL

Ph-pos ALL will be only discussed briefly as it will be dealt with in detail in a subsequent manuscript. One-quarter of all adults are Ph-pos, and the incidence is approximately 50% in patients older than age 50. Until the results of recent studies in older patients became available, most patients with Ph-pos ALL were managed with intensive chemotherapy and a tyrosine kinase inhibitor. Imatinib has improved the CR rate in a number of trials to greater than 90% and makes more patients eligible for transplant.[18] Imatinib resistance mutations are increasingly reported, and these should be sought in patients with relapsed and refractory disease.

Nearly all older patients with Ph-pos disease should be treated with a TKI, vincristine, steroid, and possibly reduced-dose anthracycline. If they achieve CR, subsequent therapy should be individually tailored depending on toxicity, comorbidities, and, possibly, MRD status. B-cell antibodies are also worth considering in this age group; rituximab is well tolerated. This de-escalation of therapy is well tolerated and highly effective in the short term, but data are lacking regarding medium- to long-term survival. An alternative and very effective strategy in older patients is to use dasatinib alone or with steroids.[19]

ISSUES OF SUPPORTIVE CARE
Infection

Unless the patient has a contraindication to quinolones, such as past *Clostridium difficile* infection, they should be used in this patient group as bacterial infection is a common cause of death in induction. Similarly, G-CSF should be routinely used to mitigate neutropenia. There is randomized controlled evidence to support this practice, albeit from an older study. Antifungal prophylaxis should be considered during induction chemotherapy, but azoles need to be used carefully to avoid excess vincristine toxicity.

HEPATOTOXICITY

Some patients older than age 50 will be treated with asparaginase; this is the major cause of induction-associated liver dysfunction. There is an association between induction-associated liver dysfunction and anthracycline use and possibly with imatinib. Patients are generally given asparaginase in the third week from the start of chemotherapy. Liver function tests should be carefully monitored, and asparaginase should not be given to patients with significantly abnormal liver function tests. Hepatotoxic drugs such as cotrimoxazole, omeprazole, and many antifungals should be stopped.

RENAL DYSFUNCTION

Many older patients have abnormal baseline renal function. Careful attention should be paid to hydration and the avoidance of nephrotoxic drugs unless there is no alternative. Allowing patients to become fluid overloaded can necessitate the later use of furosemide, which depletes intravascular fluid with downstream effects on the kidneys.

A ROLE FOR REDUCED-INTENSITY ALLOGENEIC TRANSPLANTATION?

It may seem illogical to be contemplating reduced-intensity allogeneic transplantation in a group of patients who tolerate chemotherapy poorly; however, RIC allografting, if studies

show it to be an effective way of eradicating disease, uses moderate doses of chemotherapy and involves a short period of neutropenia, mild mucositis, and is generally not very debilitating. A transplant may be seen as providing a more rapid recovery than consolidation, intensification, and longer than 2 years of maintenance chemotherapy. It is important to avoid severe graft versus host disease (GVHD) in this older age group, but RIC allografts do rely on a graft-versus-leukemia effect. The main evidence for a graft-versus-leukemia effect is that relapse is less common in patients with grade 2 to grade 4 acute GVHD and/or chronic GVHD. However, this effect is most operative in patients with low levels of disease. Full intensity conditioning causes excessive TRM in this age group and is seldom indicated. It should be noted that RIC allografts are mainstream therapy in older patients with AML with many studies showing acceptable TRM in selected patients.

Two registry-based comparisons with full intensity conditioning show adjusted survival and event-free survival to be similar to full-intensity conditioning (Fig. 4).[20,21] Unsurprisingly, relapse rates are increased and TRM only marginally decreased. The optimum conditioning regimen and GVHD prophylaxis strategy are yet to be defined.

The United Kingdom ALL XIV trial is prospectively examining the role of RIC sibling and unrelated donor allografting. All patients older than age 40 are considered high risk and are eligible for allografts if they are fit, in CR, and have a matched sibling or 8/8 molecularly matched unrelated donor. (Patients with high-risk cytogenetics or persistent MRD are permitted to have a 7/8 match). Sixty-two percent of the first 374 patients are eligible, and we have data on the first 60 allografts. Survival with a median follow-up of 12 months exceeds 80%, and the current TRM of 9% shows that the procedure can be performed safely on a multicenter basis. The rates of acute and chronic GVHD are modest (Table 3). Mixed chimerism is a common outcome of fludarabine, melphalan, and alemtuzamab allografts; 10 patients received do-

TABLE 3. Major Demographic Characteristics and Outcomes for 60 RIC Allografts

Registered for RIC transplant	91
Transplant data available	60
Median age	49
Sibling donor	36 (60%)
ECOG PS 1-2	24 (40%)
WBC >30 × 10e9/L	12 (20%)
High-risk cytogenetics	27/51*
Median time to transplant from diagnosis	5.4 months (4-9)
Acute GVHD grade 2-4	29%
Chronic GVHD	14 (23%)
Donor lymphocyte infusions	16/41**
Relapse	4 (2 survive)
Transplant-related mortality	6
Total deaths	8

Abbreviations: RIC; reduced intensity conditioning; ECOG; Eastern Cooperative Oncology Group; PS, performance status; WBC, white blood count; GVHD, graft versus host disease.
*Nine patients did not have evaluable cytogenetics.
**Data only available on 41 patients currently (10 for mixed chimerism and six for persistent or rising minimum residual disease).

nor lymphocyte infusions for this and six additional patients received donor lymphocyte infusions for persistent or progressive MRD. Fifteen of these 16 patients currently survive, but follow-up is short.

FUTURE DEVELOPMENTS

The newer agents, blinatumomab and inotuzumab,[14,16] have not been tested specifically in this age group, but there will be some data from the ongoing phase III studies (Inovate and Tower). Both drugs have been tested mainly in the relapsed/refractory setting, but blinatumomab is very impressive at converting persistent MRD positivity (after 3 months of chemotherapy) to negativity (78% of 116 patients in the phase II study).[22,23] As most older patients have dose reductions that may result in higher incidences of persistent MRD positivity, it is attractive to add in a 28-day course of blinatumomab to deepen remission states before further consolidative or maintenance chemotherapy. However, first we need data comparing this agent with conventional chemotherapy and to know if older patients tolerate the cytokine release syndrome and neurotoxicity. Similarly, the efficacy and safety of inotuzumab will need to be compared with conventional salvage therapy before we can assess the place of this drug in older patients.

In the United Kingdom, we are working to establish a backbone of chemotherapy that older patients can tolerate, with reasonable CR rates and 1-year survival. We then plan to add in novel agents to improve those outcomes without increasing toxicity and NRM. The collection of diagnostic specimens in these patients and correlation with clinical data may improve our understanding of the biologic differences that exist in older patients with ALL.

FIGURE 4. Preliminary Results of Reduced Intensity Allografting from United Kingdom ALL XIV
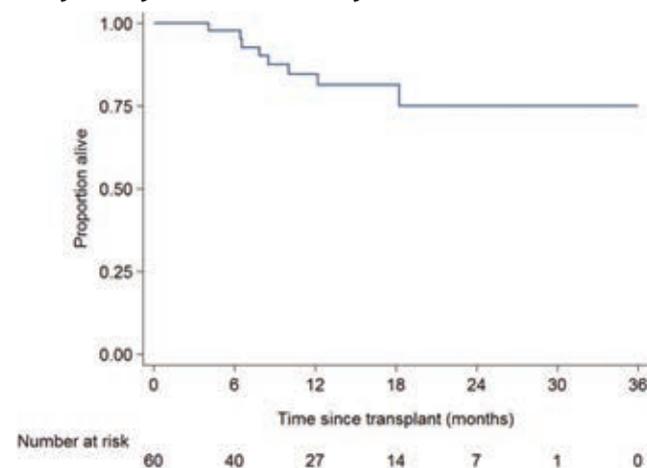
Overall survival post-transplant.

Chimeric antigen receptor T cells directed against CD19 have shown remarkable efficacy in a relatively small number of children but are likely to be tested in younger adults before any trials in the older-patient population.[24] A proportion of patients experience severe cytokine release syndrome requiring ICU admission; this could be a limiting factor in the older age group.

CONCLUSION

Effective management of older patients with ALL is a major unmet need. The different biology of the disease and the patient is recognized, and we now need the systematic trials that have improved the outcome of ALL in children and adults to be applied to the older age group. Many fit patients between age 50 and 65 will be able to tolerate conventional aggressive chemotherapy with reasonable outcomes and acceptable NRM. However, older and less-fit patients require less-aggressive chemotherapy, and strategies are needed to improve CR rates in this group. It is essential that we better understand the comorbidities that affect tolerance to chemotherapy so that we can rationally adjust therapy and not rely on end-of-the-bed impressions. Trials such as the United Kingdom ALL 60+ study that assess comorbidities and include objective and subjective QOL endpoints will hopefully advance the field. Leukemia physicians are urged to enter older patients into trials in order that we may improve the outcome of this difficult clinical management problem.

ACKNOWLEDGEMENT

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Treatment of Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia in Adults: A Broader Range of Options, Improved Outcomes, and More Therapeutic Dilemmas

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OVERVIEW

The article addresses selected key areas of flux in the management of Philadelphia chromosome–positive acute lymphoblastic leukemia. There is no doubt that tyrosine kinase inhibitors (TKIs) have made a major contribution to higher rates of complete remission and that more patients are now surviving long term. Many patients tolerate TKIs well, and remission can be achieved with minimal toxicity. Because remissions can include a proportion of patients who become *BCR-ABL1* transcript negative, the question of whether allogeneic hematopoietic stem cell transplantation can be avoided requires discussion. Despite the major progress that has been made and the relative profusion of therapeutic choice compared with 10 years ago, evidence is still lacking for many of the major possible interventions, and how to combine them is unclear. Because of the rarity of the condition and the enticing possibility of increasing traction to therapy, clinical trials and international cooperation remain paramount.

Acute lymphoblastic leukemia (ALL) in which the Philadelphia (Ph) chromosome t(9;22) is detected (i.e., Ph+ ALL) is a genetically, biologically, and clinically distinct subtype of B-precursor ALL, and it comprises approximately 20% of the total ALL incidence. The incidence of Ph+ ALL increases with age, from less than 5% in younger children to 20% to 25% in older adults,[1,2] although population-based studies indicate that the incidence does not continue to increase beyond the fourth decade.[3] Standard ALL chemotherapy treatment alone results in a complete remission (CR) rate of at least 10% lower than in Ph-negative ALL,[4,5] with a median survival of around 8 months.[2] However, in recent years, the addition of TKIs to remission induction treatment—combined with earlier and more frequent allogeneic donor identification, facilitating allogeneic hematopoietic stem cell transplantation (alloHSCT)—has made a considerable change to the outcome. However, the relatively rapid expansion of the range of realistic therapeutic possibilities in an uncommon disease has generated some genuine therapeutic dilemmas in an arena where testing all of the possibilities in well-designed trials has not yet occurred. Furthermore, there is international variability and even local variability in the availability of some of the therapeutic options and of what may be considered standard-of-care choices in some geographic locations is not relevant to others. In this summary, I will focus on key decision points in the treatment of Ph+ ALL, posing the relevant therapeutic questions and evaluating evidence that supports common approaches. I will highlight areas in which there is no clear best practice, providing my personal opinion only when no prevailing consensus exists.

WHAT ARE THE KEY POINTS IN THE PRETREATMENT WORK-UP?

This is a rare disease. As many patients as possible should be offered the opportunity for referral to a major treatment center as soon as possible when ALL is suspected. Even so, diagnostic adequate work-up for Ph+ ALL is straightforward and within the reach of most centers. All patients with ALL should be evaluated urgently for the presence of the Ph chromosome by conventional cytogenetics, fluorescent in situ hybridization, and reverse transcriptase polymerase chain reaction (RT-PCR) for *BCR-ABL* p190 and p210 transcripts. The absolute number of *BCR-ABL* transcripts should be quantified relative to a housekeeping gene, usually *GUS* or *ABL*, using real-time quantitative PCR. p210 quantification is standardized internationally because of its routine use in chronic myeloid leukemia (CML) monitoring, whereas p190 quantification is not standardized, and interlaboratory variation in methods and results can occur.[6] ABL kinase domain mutations at diagnosis that are likely to render resistance to TKIs have been identified by deep sequencing,[7,8] but they typically are not detected by current conventional ap-

proaches. Because their clinical significance is undetermined, they currently cannot be used to direct initial therapy.

HOW TO INDUCE COMPLETE REMISSION IN PH+ ALL

Traditional chemotherapy regimens result in a low CR rate and poor outcome, but, despite the lack of randomized studies over the past 10 years, overwhelming evidence of a higher rate of CR and a long-term survival benefit with the addition of TKIs to chemotherapy regimens has emerged. Most of these studies have been conducted with imatinib at doses between 400 mg and 800 mg daily. The German Multicenter Acute Lymphoblastic Leukemia (GMALL) study evaluated imatinib alternating with or concurrent to induction chemotherapy in 92 patients who had de novo Ph+ ALL. CR was achieved in 95% of patients, and the 2-year overall survival (OS) rate was 36%.[9] The University of Texas MD Anderson Cancer Center (MDACC) used a hyperCVAD regimen in combination with imatinib in patients with de novo or minimally treated Ph+ ALL, resulting in 3-year OS rate of 54%.[10] Yanada et al[11] reported CR rates of 96% in 80 patients (70% achieved *BCR-ABL1* transcript negativity) compared with 51% in historic controls.[11] The 1-year event-free survival (EFS) and OS rates were 60% and 76%, respectively. The Northern Italian Leukemia Group (NILG) reported a CR rate of 92% in 59 patients with newly diagnosed Ph+ ALL using short pulses of an imatinib/chemotherapy combination; 5-year OS and disease-free survival (DFS) rates were 38% and 39%, respectively, compared with 23% and 25%, respectively, in historic controls.[12] The U.K. ALL12/E2993 study[13] was the most recent to report and was the largest of its type (175 patients treated with imatinib added to standard therapy and compared with a large historic cohort of 266 patients treated on the same trial in the preimatinib era). The study showed a considerable survival advantage for an imatinib-containing regimen. The earlier addition of imatinib during therapy resulted in the best outcome.[5] The data are discussed in more detail later in this chapter. There is no rationale now for treating Ph+ ALL without a TKI.

WHICH TKI IS OPTIMAL FOR FRONT-LINE THERAPY?

Studies reporting the use of a TKI other than imatinib as front-line therapy are in the minority,[14,15] but some studies are ongoing (e.g., the European Working Group on ALL study of dasatinib and chemotherapy induction in older persons[16]). There are theoretical differences between the TKIs in *BCR-ABL1* kinase domain binding, potency of *BCR-ABL1* kinase inhibition (e.g., nilotinib and dasatinib are more potent than imatinib), and activity against non–tyrosine kinases (e.g., dasatinib is active against *SRC* kinases). Ponatinib has potential activity against polymutant *BCR-ABL1* alleles, which occur (at least in CML) after the progressive exhaustion of the pool of unmutated *BCR-ABL1* alleles over the course of sequential TKI therapy.[17] Researchers at the MDACC have evaluated and published data from sequential trials with imatinib,[10] dasatinib,[14] and ponatinib, a potent pan–*BCR-ABL1* TKI,[18] each in combination with hyperCVAD, with no clearly elucidated difference between them to date. No direct comparison has been evaluated, and—to my knowledge—no ongoing clinical study is addressing the question of which is the best initial TKI. I would like to direct the readers to well-researched and carefully concluded evidence-based guidelines for TKI use in ALL, which have recently delineated the Canadian perspective on this matter and which provide more detail than can be given here.[19]

CAN PH+ ALL BE TREATED WITHOUT CHEMOTHERAPY?

Induction chemotherapy for ALL is not without toxicity; a number of patients, regrettably, succumb to complications. Sepsis during the neutropenic period of induction therapy is a common precursor to serious morbidity and mortality. Mortality varies with age but is rarely less than 5%[20,21] and can be as high as 15% to 20% in older people.[21,22] Vignetti et al[23] were the first to report data on chemotherapy-free induction therapy for Ph+ ALL.[23] The LAL0201-B trial from the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) study included only patients older than age 60, with a median age of 69. Imatinib (800 mg/day) was given with prednisolone. The CR rate was 100%, with minimal toxicity, and the median survival was 20 months, with a 12-month OS of 74%. Postremission therapy and long-term outcomes were not reported. A further study from the same group, GIMEMA LAL1205, showed a similarly high CR rate with no mortality when dasatinib was combined with a corticosteroid alone as induction.[15] Interpretation of those studies will be

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KEY POINTS

- The outcome of treatment of Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) has changed considerably for the better over the last 10 years, with up to 60% 5-year overall survival rates with tyrosine kinase inhibitor (TKI) induction followed by allogeneic hematopoietic stem cell transplantation (alloHSCT).
- Complete remission can now be achieved with minimal toxicity TKIs with little or no chemotherapy, but the long-term outcome of chemotherapy-free induction regimens is not known.
- The optimal TKI for induction of remission is not known.
- *BCR-ABL1* transcript monitoring demonstrates that complete molecular remission can be achieved in some patients. Whether this may indicate that future treatment intensification with alloHSCT can be omitted or reserved for disease progression is a totally open question.
- Presently, alloHSCT retains an important role in the management of Ph+ ALL; nonmyeloablative conditioning regimens are now widely used, but results of prospective evaluations of this strategy are still unknown.

confounded by the heterogeneous therapy given subsequently. An ongoing trial, GIMEMA LAL 1509, used a similar chemotherapy-free induction with dasatinib and corticosteroid induction treatment, but added chemotherapy and/or alloHSCT for patients who did not reach a sustained complete molecular response (CMR; i.e., no detectable *BCR-ABL1* transcripts). This approach has been reported so far only in abstract form,[24] but the results are very interesting. The CR rate was 97%, with no induction-related deaths, which included CMR in 18%. Interestingly, *BCR-ABL1* p210 (45% of cases in the report) had a worse prognosis, with lower initial susceptibility to TKIs and a 58% incidence of relapse. The report provocatively suggests that the subset of patients who had deep molecular remissions may be spared further intensive treatment. The long-term follow-up of this study will be of major importance to the field. A recently completed, but also not yet published, study (GRAAPH-2005) from the French Group for Research on Adult Acute Lymphocytic Leukemia Study (GRAALL) also highlights the value of a lower intensity of chemotherapy during induction. Chalandon et al[25] randomly assigned 265 previously untreated patients with Ph+ ALL to receive induction with imatinib/hyperCVAD or imatinib with dexamethasone/vincristine (DIV). Very high CR rates were noted in both arms (DIV, 98%; hyperCVAD, 91%); the lower CR rate in the hyperCVAD arm was a result of higher induction mortality.[26] DIV induction was noninferior to hyperCVAD, with no difference in 3-year EFS (46% vs. 38%; p = 0.25) and OS (53% vs. 49%; p = 0.61).

Although the long-term outlook of treating patients without chemotherapy is unknown, this is a reasonable treatment approach in older patients and should be considered. A detailed discussion of the treatment of older people with ALL in general is given in the chapter by Dr. David Marks.

WHAT IS THE MOST APPROPRIATE CNS-DIRECTED THERAPY IN PH+ ALL?

A small proportion of patients with ALL will present with central nervous system (CNS) disease,[27] but all will need prophylaxis. Recent data using sensitive detection of ALL cells in the cerebrospinal fluid (CSF) suggest that higher-than-expected proportion of patients (18%) present with occult ALL cells in the CSF.[28] This did not emerge as a clinically relevant problem in the series studies, which suggests that therapy directed at preventing the emergence of CNS disease has been and will remain a very important component of the treatment of ALL. Traditionally, a combination of intrathecal therapy, high-dose systemic therapy that crosses the blood-brain barrier, and irradiation has been used and has resulted in a very low level of CNS relapse. However, CNS relapse, when it does occur, portends a very poor prognosis.[29] Typically, patients with Ph+ ALL have been referred for myeloablative HSCT wherever possible and have benefitted from total-body irradiation. However, as we consider chemotherapy-free treatment approaches and reduced-intensity conditioning (RIC) regimens for alloHSCT, the opportunities for CNS-directed prophylaxis to be built-in to the typical protocol are not always obvious. Treating physicians and trialists alike need to consider this issue carefully in an area of practice that does not have a strong evidence base. Imatinib and nilotinib do not cross the blood-brain barrier; dasatinib does and is reportedly part of an effective therapy,[30] and ponatinib has been reported to cross the blood-brain barrier in a murine model.[26] However, there are no trial data to support using TKIs as CNS-directed prophylaxis. CNS irradiation now—and rightly—is little used because of toxicity, but it remains unclear whether systemic methotrexate can be dispensed with, even if the approach is a chemotherapy-free one. The clear benefit of high-dose methotrexate on prevention of CNS relapse has never been demonstrated; there is considerable variability in the dose and number of courses used, so there is little firm evidence on which to select this therapeutic component. It may be safest to be assiduous with intrathecal therapy. The total number of intrathecal treatments needed to constitute an appropriate course of therapy is also unclear. However, if patients quickly move from induction to nonmyeloablative alloHSCT, its unlikely they will have had sufficient intrathecal therapy, so resumption after HSCT may be wise.

WHAT IS THE OPTIMAL POSTREMISSION THERAPY? Myeloablative AlloHSCT: Is It Still the Cornerstone of Definitive Therapy for Ph+ ALL?

The cornerstone of postremission therapy for Ph+ ALL traditionally has been myeloablative alloHSCT (reviewed in Fielding[31]). The strongest support for the overall benefit of sibling alloHSCT in unselected patients with Ph+ ALL comes from the two largest studies conducted in this disease. The LALA-94 trial[4] showed that, among 103 patients eligible for HSCT, the availability of a sibling allogeneic donor was independently predictive of remission duration. An analysis of treatment received in the U.K. ALL12/E2993 trial[5] in 267 patients showed that patients with Ph+ ALL who received sibling or unrelated donor myeloablative alloHSCT had a much better outcome than those receiving chemotherapy alone. Fewer than 30% of the study population were able to receive allogeneic HSCT, mostly because of older age or failure of existing therapy to generate a CR.

Although any data on the outcome of alloHSCT must be interpreted with caution, because of the problems of selection bias and immortal time bias, the weight of evidence in the pre-TKI era has been interpreted in favor of myeloablative HSCT using either a sibling or unrelated donor in adults with Ph+ ALL who have experienced first complete response (CR1).

CAN WE TREAT PH+ ALL WITHOUT TRANSPLANTATION?

With the advent of the genetically targeted treatment that can generate, at least in a proportion of patients, a negative *BCR-ABL1* transcript response, the possibility of dispensing with

alloHSCT, which would be a major advance, must be considered. Evidence in support of this has so far been gathered in patients in whom alloHSCT has not been possible; these patients are never a comparable group to those in whom alloHSCT could be and was performed. Nonrecipients are typically older, have more comorbidities, and are more likely to have experienced relapse by the median time to alloHSCT.[5,13]

Studies in which alloHSCT was not the primary focus may nonetheless contribute to our understanding of its role. As always, though, the circumstances under which patients did not receive alloHSCT must be taken into account. One of the first studies to suggest omission of alloHSCT as a realistic possibility in the TKI era was a Children's Oncology Group study in which patients up to age 21 were treated with imatinib added to chemotherapy.[32] Postremission treatment with sibling alloHSCT was included in the protocol, but the trial did not allow for matched unrelated donor (MUD) alloHSCT on the basis of a previous, international study in children[33] that showed a 43% treatment-related mortality (TRM) for MUD alloHSCT. Hence, this study left a small cohort of children who received an imatinib/chemotherapy combination without alloHSCT. There was relatively high rate of off-protocol MUD alloHSCT that confounded data interpretation. However, at 3 years, the outcomes for those treated with imatinib/chemotherapy (25 patients) compared favorably with those treated with alloHSCT (21 patients); the 3-year DFS without alloHSCT was 85%. Although the study was neither designed nor powered to answer the question of whether imatinib/chemotherapy could replace sibling alloHSCT for children with Ph+, the data introduced the hypothesis that children with Ph+ ALL can be treated successfully without alloHSCT. In combination with emerging data of improved overall outcomes for adults with Ph+ ALL, this study has reasonably sparked consideration of the omission of alloHSCT from treatment. A multivariate analysis of patients treated at the MDACC with hyperCVAD and TKI regimens,[34] which excluded those who had received alloHSCT, revealed that achievement of major molecular response (MMR), namely a BCR-BCR-ABL ratio of < 0.1, was associated with better survival outcomes. However, the selection of the MMR as a cutoff remains somewhat arbitrary, although it is explained in the paper, and the numbers of patients on whom this analysis is based are limited. The authors reasonably take the data to support the role of minimal residual disease (MRD) monitoring but wisely do not suggest that these data currently support the omission of alloHSCT.

In my opinion, the most robust evidence to date on the present need to continue considering alloHSCT as a core therapy comes from trials groups that have reported on the outcome of patients who received chemotherapy and a TKI alone and have been able to compare that group with those who received alloHSCT. Among the few published studies to report on the outcome of a substantial group of patients of transplantable age who did not undergo transplantation was the ALL202 trial from the Japanese Adult Leukemia Study Group,[11] in which the combination of imatinib and chemotherapy was evaluated in 80 adult patients, 31 of whom did not undergo alloHSCT. When compared with historic controls in whom there were no event-free survivors at 24 months, the 2-year estimated EFS was significantly better for those patients receiving imatinib as part of their therapy. In the largest such study internationally, the Ph+ arm of the U.K. ALL12/E2993 trial examined the outcome of treatment in 266 patients enrolled on the preimatinib era and was compared with the outcome in 175 patients receiving the same chemotherapy treatment and alloHSCT approach but with the addition of imatinib.[13] There was a large and statistically significant outcome benefit with imatinib cohort; at 4 years, the OS of all patients in the imatinib cohort was 38%, versus 22% in the preimatinib cohort. However, the rate of alloHSCT was 46% in the imatinib cohort and was 31% in the preimatinib cohort.[13] This raises the question of what proportion of the benefit accrued was a direct result of imatinib alone, rather than the contribution made by imatinib to a significantly better initial therapeutic response facilitating more frequent alloHSCT. A Cox multivariate analysis, which took alloHSCT into account, showed only a modest additional benefit with the addition of imatinib (hazard ratio for EFS, 0.64; 95% CI, 0.44 to 0.93; p = 0.02). Importantly, there was significant benefit for OS and RFS. The investigating team, of whom I was a member, concluded that the addition of imatinib to standard therapy considerably improved the CR rate and long-term OS for adults with ALL. However, our data showed that a proportion of the OS benefit derived from imatinib facilitation of alloHSCT. Studies in which the long-term outcome of patients who have been selected by good risk criteria to postpone alloHSCT will eventually inform a more strategic deployment of alloHSCT in this disease. Additionally, non-alloHSCT immunotherapies, such as the bispecific antibody against CD19 and CD3, blinatumomab,[35] and chimeric antigen receptor T cells (discussed in the companion article by Sadelain et al), may find a role in postremission therapy of high-risk ALL as a potential alternative to alloHSCT.

UNDER WHAT CIRCUMSTANCES SHOULD WE USE NONMYELOABLATIVE (REDUCED-INTENSITY CONDITIONED) ALLOHSCT?

As an alternative to no transplantation for patients who are beyond the upper age limit for myeloablative alloHSCT or who have comorbidities that rule it out, nonmyeloablative (RIC) alloHSCT is used increasingly widely. Retrospective reports constitute the only evidence base to date, although the United Kingdom National Cancer Research Institute Adult ALL subgroup U.K. ALL14 trial includes a prospective evaluation of RIC alloHSCT. Most published series of RIC include patients beyond CR1, and none confine themselves to Ph+ ALL.

A few key, positive messages regarding RIC alloHSCT in Ph+ ALL emerge from the studies reported to date.[37-43] First, RIC can be used, with an acceptable early TRM in patients who are older than those suitable for a myeloablative approach. The median ages reported range from 38 to 50 years, and treatment-related mortality in more recent studies,

which include more patients in CR1, is consistently between 20% and 30%. Currently, no particular conditioning regimen can be considered optimal. Chronic graft-versus-host disease (cGVHD) rates are high, and there is insufficient evidence to determine whether the high rate of GVHD is positively associated with a better disease-related outcome. There likely is scope for approaches in which conditioning regimens that have lower risks of cGVHD are investigated. In summary, nonmyeloablative allogeneic HSCT approaches appear promising and offer DFS rates in Ph+ ALL that, when overtly specified, appear higher than those obtained with chemotherapy and imatinib alone and are in line with what has been achieved by using myeloablative approaches. Two large studies from the IBMTR and EBMT registries reported the comparative outcomes of myeloablative versus RIC alloHSCT in patients with ALL. Ph+ disease was excluded from the IBMTR analysis. The EBMT analysis[44] included 145 patients with Ph+ ALL; among that subgroup, OS was 47% ($\pm$ 5%) for myeloablative conditioning versus 40% ($\pm$ 9) for RIC. In the multivariate analysis of the whole population, the nonrelapse mortality was lower in RIC recipients (hazard ratio, 1.98; p = 0.0001), whereas relapse risk was higher. Multivariate analysis showed that the type of conditioning regimen was not significantly associated with leukemia-free survival. In the IBMTR study,[45] which only included patients with Ph-negative ALL, no independent effect of conditioning intensity was seen. Importantly, all reports of RIC alloHSCT in ALL show poor outcomes when used beyond CR1.

HOW SHOULD TKI BE USED FOLLOWING ALLOHSCT?

The necessity for TKIs after alloHSCT and the duration, if used, is unknown. When studies have specifically reported, TKIs are described as hard to tolerate immediately after alloHSCT. Only one study has addressed this question directly. The German Multicenter Adult ALL Group carried out a prospective, randomized, multicenter trial that compared the tolerability and efficacy of post-transplantation imatinib administered either prophylactically (26 patients) or only after detection of BCR-ABL1 transcripts (29 patients).[46] The study did not find any difference in outcome between the two arms, but it was noted that, when given prophylactically starting at 3 months after alloHSCT, it was hard to tolerate, and not all patients were able to continue. Early or high-level reappearance of BCR-ABL1 transcripts after alloHSCT identified a small subset of patients who did not benefit from the addition of imatinib. Regular monitoring of BCR-ABL1 transcripts is arguably the most important component of the therapy. Although bone marrow provides a higher sensitivity of detection than blood, it is feasible to monitor blood more regularly. In my personal practice, I do not routinely administer a TKI after alloHSCT in the absence of detectable BCR-ABL transcripts, but I monitor BCR-ABL1 transcripts monthly in peripheral blood and immediately carry out a bone marrow assessment if transcripts are detected.

IS THERE ANY ROLE FOR AUTOLOGOUS STEM CELL TRANSPLANTATION?

In the largest study of adult ALL ever, U.K. ALL12/E2993, autologous stem cell transplantation (autograft) was compared with chemotherapy in a randomized manner. Chemotherapy was statistically significantly superior.[47] Nonetheless, the concept of high-dose therapy and return of autologous cells continues to be realized under certain circumstances,[48] and studies have reported good outcomes under particular circumstances in which patients are MRD negative[49] at the time of treatment and, usually, continue to receive a TKI. To what extent the autograft contributed to the good outcomes is not clear, because other studies report long-term outcomes in selected patients who are MRD negative and continue to receive TKIs who did not have autografts.

ADDITIONAL PROGNOSTIC INFORMATION

Additional genetic information can provide prognostic refinement in Ph+ ALL. High-resolution single nucleotide polymorphism (SNP) arrays identified alterations in the transcription factor gene IKZF1 (IKAROS) essential for lymphoid proliferation and differentiation. IKZF1 deletions, identified in greater than 60% of patients with Ph+ ALL, partly explained the aggressive nature of the disease.[50] At present, these are not actionable genetic lesions. For physicians whose patients are not enrolled in trials and who are struggling with individual alloHSCT decisions, these may be relevant factors in decision making.

WHAT SHOULD BE MONITORED AND HOW CAN IT BE INTERPRETED?

Monitoring of Ph+ ALL by quantification of BCR-ABL1 transcripts offers a sensitive and specific way of detecting and monitoring disease. The concepts of CMR or MMR, as used in the assessment of patients with CML, often are cited. The clear relevance in CML relates to the internationally standardized therapy, so responses can be compared among patients and among centers. This is far from the case in Ph+ ALL; hence, the level of response and its predictive value are only relevant to the therapeutic scenario in which they have been reported. I urge caution in extrapolating data described in terms of these definitions beyond the original reporting conditions.

WHAT CAN BE DONE FOR PATIENTS WITH RELAPSED PH+ ALL?

The outcome of relapsed ALL in adults is poor.[29,51,52] Most large studies of relapsed ALL show that factors at diagnosis, such as cytogenetics, do not strongly influence the outcome once relapse has occurred. Time since diagnosis and age are the two strongest predictors of relapse outcome when considering chemotherapy and alloHSCT as therapies. A shorter duration of first remission and older individual age lower the

chance of a good outcome. However, in the TKI era, the mechanisms of resistance are reasonably well studied. At relapse of Ph+ ALL, it is possible now for patients to progress through newer generations of targeted agents in a systematic fashion according to the results of mutational analysis of *BCR-ABL1* transcripts. Patients in whom imatinib ceases to produce a response may respond to nilotinib[53] or dasatinib,[54] and there is even an option, ponatinib, for patients with the T315I mutation.[55] Although TKIs are not without adverse effects, and ponatinib in particular carries a risk of cardiovascular events, they are nonetheless a vastly superior option to rounds of myelosuppressive chemotherapy in preserving performance status and being available to and tolerated by patients in the older age range. There is no evidence of long-term survival mediated by TKIs after relapse. Nonetheless, the difference between EFS and OS in relapsed Ph+ ALL is moving apart. Studies should continue to carefully record both, and readers should pay attention. In addition, results with allografts are being reported. Although allografts have uncertain long-term benefits, there are case reports of good outcomes. Immunotherapy without alloHSCT also is an option for the treatment of relapsed ALL. An international,

phase II trial of blinatumomab in patients with Ph+ ALL who have experienced relapse after treatment that included a minimum of two lines of TKI therapy has recently been completed, and analysis is underway. Patients with Ph+ ALL can respond to CD19 CART cell therapy.

PH-LIKE ALL

In the so-called Ph-like ALL, t(9;22) is absent, but the leukemia is characterized by a range of genomic alterations that activate a limited number of signaling pathways similar to those activated in Ph+ ALL,[56] some of which may be amenable to inhibition with approved TKIs. The precise definition of these targetable, kinase-activating lesions in clinical practice using standard techniques is not yet clear, but suggested algorithms have emerged that provide practical advice on when and how to consider this subtype of ALL.[57] TKIs have yet to be formally evaluated, except in case reports.[58] Nonetheless, there will be patients in whom physicians wish to consider a TKI as an option, and requests for insurers or health systems to reimburse these agents will have to be taken into account soon.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked "L" indicate leadership positions. Relationships marked "I" are those held by an immediate family member; those marked "B" are held by the author and an immediate family member. Institutional relationships are marked "Inst." Relationships marked "U" are uncompensated.

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CD19 CAR Therapy for Acute Lymphoblastic Leukemia

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OVERVIEW

Chimeric antigen receptor (CAR) therapy is an emerging immunotherapy that shows great promise for cancer, in particular acute lymphoblastic leukemia (ALL). CARs are recombinant receptors for antigen, which, in a single molecule, redirect the specificity and function of T lymphocytes. Following their genetic transfer to patient T cells, the latter acquire the ability to recognize leukemia cells and destroy them. Several years ago, we identified CD19 as an attractive target for CAR therapy for most B cell malignancies, including ALL. We and others have reported remarkable clinical outcomes in adults and children with ALL, achieving a high complete remission rate irrespective of age, prior treatments, or other prognostic markers. Severe cytokine release may develop in patients with high tumor burdens. Several interventions are available to curb the cytokine release syndrome when it occurs. Based on the impressive results obtained with CD19 CAR therapy for ALL, it is realistic to expect that CD19 CARs will become part of the armamentarium for B cell-ALL and other B cell malignancies.

Chimeric antigen receptors (CARs) are recombinant receptors for antigens, which in a single molecule, redirect the specificity and function of T lymphocytes. A general premise for their use in cancer immunotherapy is to rapidly generate tumor-targeted T cells, bypassing the barriers to and incremental kinetics of active immunization.[1] Second generation CARs not only redirect cytotoxicity, but also reprogram T cell function and longevity, thus conferring supraphysiological properties on T cells, which then become "living drugs" that exert both immediate and sustained therapeutic effects.[2]

T cells normally recognize their target antigen through the T cell receptor (TCR), which binds to human leukocyte antigen (HLA)-peptide complexes displayed on the surface of target cells. The TCR does not itself signal, but it does determine, based on its affinity for the HLA-peptide complex, the strength of the activation signals the T cell generates on contacting the tumor. The strength of these signals is further modified by costimulatory receptors, which may be either activating (such as CD28 and 4–1BB) or inhibitory (such as CTLA-4 and PD-1).[3] The ligands for these receptors are not ubiquitously expressed, and therefore place costimulation under the control of the target cell engaged by the T cell. Thus, professional antigen presenting cells, such as B cells and dendritic cells, may express powerful ligands for CD28 and 4–1BB, but tumors typically do not, as is the case for ALL. The concept underlying second generation CARs is to provide costimulatory support to T cells irrespective of the presence of a ligand on tumor cells (Fig. 1). In this context, T cells that engage the tumor through the CAR are given a costimulatory signal within the tumor microenvironment itself, resulting in a pharmacologic boost that we thought would radically alter the functional profile of T cells.[4] The CARs that have recently shown impressive clinical outcomes in patients with B cell malignancies, especially ALL, are indeed second generation CARs.

CAR TARGETS AND THE CD19 PARADIGM

Unlike the physiological TCR, which engages HLA-peptide complexes, CARs are able to engage native cell surface molecules and do not require any processing or HLA expression to be recognized. CARs therefore can recognize target antigens on any HLA background, in contrast to TCRs, which need to be matched to the patient's HLA haplotype. Furthermore, CARs can target tumor cells that have downregulated HLA expression or proteasomal antigen processing, two mechanisms that contribute to tumor escape from TCR-mediated immunity.[5] Another attractive feature of CAR-mediated T cell responses is that they are not limited to proteins and may target carbohydrate and glycolipid structures. The target must, however, be found on the tumor cell surface.

Identifying appropriate CAR targets is important to achieving complete tumor eradication, as is avoiding damage to normal tissues that express the same target antigen ("on-target, off-tumor effect"). Two decades ago, we selected CD19 as the prime target for developing our CAR technology. CD19 is a cell-surface antigen found on most B lineage lymphomas and leukemias.[6] We chose CD19 not only because it is highly expressed in these tumors, but also for its highly restricted expression in normal tissues. CD19 is indeed known to be only expressed among normal tissues in

FIGURE 1. TCR and CAR Structure
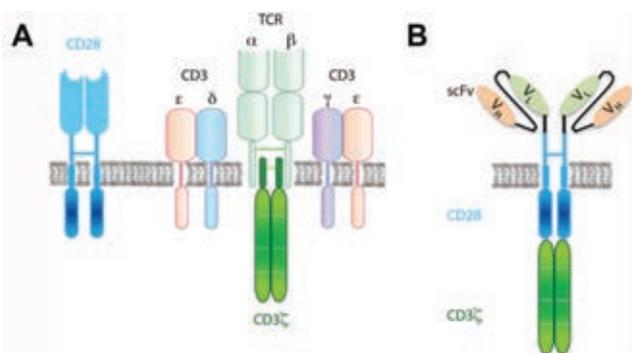
A: Physiological T cell activation is mediated by the heterodimeric T cell receptor (TCR) in association with the CD3 complex (which comprises the gamma, delta, epsilon, and zeta chains) and modulated by a multitude of costimulatory receptors, such as CD28. B: In contrast, CARs possess, in a single molecule, the ability to trigger antigen specific T cell functions through three critical domains: a single-chain variable fragment (scFv) (at the top), which mediates antigen recognition; the CD3 zeta chain (green), which initiates T cell activation; and a costimulatory domain (here CD28, in blue), which is lacking in first generation CARs and is a hallmark of second generation CARs.

TABLE 1. Outcomes of Patients with ALL Treated with CD19 CAR Therapy

Publication/Meeting Date	Number/Age of Subjects	Complete Remission Rate
Brentjens, *Sci Transl Med*[17] March 21, 2013	5 (adults)	100%
Grupp, *N Engl J Med*[18] April 18, 2013	2 (children)	100%
Davila, *Sci Transl Med*[19] February 19, 2014	16 adults	88%
Lee, *Lancet*[20] October 13, 2014	21 (children)	67%
Maude, *N Engl J Med*[21] October 16, 2014	30 (25 children, 5 adults)	90%
Park, ASCO-2015 May 30, 2015	33 adults	91%

the B cell lineage. Thus, a successful therapy would be expected to induce a B cell aplasia, which was indeed observed in murine models[7,8] and later in patients treated with CD19 CAR therapy. Furthermore, we thought that the role of CD19 in B cell development may extend to a role in tumor survival, which would ensure that CD19 is expressed on most malignant cells and uncommonly lost.[6,9] We provided the first proof of principle that CAR-modified human peripheral blood T cells targeted to CD19 could eradicate a broad range of B cell malignancies, including ALL, using immunodeficient mice bearing medullary and systemic disease. In these mice, a single intravenous infusion of CD19 CAR–targeted T cells could eradicate a tumor and induce long-term remissions.[10] Successful B cell tumor eradication was eventually obtained with a range of different CD19 CARs,[11-15] paving the way for several ongoing clinical trials.

KEY POINTS

- CAR therapy is an emerging immunotherapy based on engineering of T cells.
- Second generation CARs, which provide costimulatory support to engineered T cells, have transformed the prospects of adoptive cell therapy.
- CD19 CARs have induced dramatic complete responses in patients with relapsed, chemorefractory ALL.
- The two toxicities of CD19 CAR therapy are B cell aplasia (destruction of normal cells that express CD19) and sCRS (which occurs in some patients following in vivo activation of the infused CAR T cells).
- It is reasonable to anticipate that CD19 CAR T cells will become part of the armamentarium for B-cell ALL and other B cell malignancies.

CD19 CAR THERAPY FOR ALL

We reported the first clinical results obtained with CAR therapy for patients with ALL more than 2 years ago by utilizing 19–28z, a second generation CAR that we transduced in autologous peripheral blood T cells collected by apheresis.[16] After enrolling adult patients with relapsed chemorefractory disease, we treated them with an infusion of 3 million CAR T cells per kg following a single infusion of cyclophosphamide (3 g/m^2) as chemotherapy conditioning. Four out of four patients with measurable disease went into molecular remission within 4 weeks.[17] We and two other groups (from the Children's Hospital of the Philadelphia and National Cancer Institute [NCI]) subsequently published follow-up studies in adult and pediatric publications, summarized in Table 1.[18-21] Results obtained at the three different centers all reported a highly remarkable complete remission rate–a rare occurrence for phase I studies in oncology, especially considering the dire prognosis of patients with relapsed ALL, particularly in adults. Although these studies follow the same overall procedure (apheresis, CAR transduction, T cell infusion following chemotherapy conditioning), they differ in several regards, including the CAR design (CD28/CD3-zeta dual-signaling domain utilized at NCI and Memorial Sloan Kettering Cancer Center [MSKCC], 4–1BB/CD3 zeta utilized at the University of Pennsylvania), T cell manufacturing, conditioning chemotherapy, patient age, tumor burden, tumor chemotherapy sensitivity, and T cell dosage.[22] Despite these variances, the comparable outcomes speak to the extraordinary robustness of CD19 CAR therapy in ALL.

At the 2015 ASCO Annual Meeting (May 29–31, 2015), Dr. Jae Park will report on 33 adult patients treated at MSKCC, of which 32 patients are evaluable for response. The median age was 54 (range, 22 to 74). Twelve patients (36%) had Philadelphia-positive ALL, 11 patients (33%) had prior allogeneic stem cell transplant (alloSCT), and 14 patients (42%) had at least three prior lines of therapy. At the time of the

CAR T cell infusion, 16 patients had morphologic disease (> 5% blasts in brain marrow) and the remaining 16 patients had minimal residual disease (MRD). Thirteen out of sixteen patients with morphologic disease (81%) and 16/16 patients with MRD (100%) were in complete remission (CR) after the 19–28z CAR T cell infusion, yielding an overall CR rate of 91% (29/32 patients). Of the 28 evaluable patients with MRD, the MRD negative CR rate was 82%. Eleven patients underwent alloSCT following the CAR T cells infusion. As of January 25, 2015, the median follow up was 5.1 months (range, 1.0 to 37.6 or longer), with 14 patients having at least 6 months of follow-up. The 6-month overall survival (OS) rate of all patients was 58% (95% CI, 36 to 74). Among the patients who achieved CR, OS at 6 months for patients who had alloSCT versus no alloSCT following CAR T cell infusion was 70% (95% CI, 33 to 89) and 61% (95% CI, 29 to 82; p = 0.30), respectively. Two patients relapsed with CD19-negative disease (6%).

The two main safety concerns associated with the use of CARs are the targeted destruction of normal tissues and strong cytokine responses occurring in a subset of patients, now referred to as severe cytokine release syndrome (sCRS).[19] The immune-mediated rejection of normal tissues that express the targeted antigen (referred to as an on-target, off-tumor response) results in B cell aplasia in the case of CD19 CAR therapy. B cell aplasia can be effectively managed by administering intravenous immunoglobulin. Furthermore, B cell aplasia is reversible following the disappearance of CAR T cells and after bone marrow transplantation. It remains an issue in those few patients who show very long-term persistence of the CAR T cells.

The second major concern is that of sCRS, which is associated with intense antitumor responses mediated by large numbers of activated T cells. These typically cause high fever (>38°C for >3 days), hypotension, respiratory distress, and/or neurological symptoms (in particular confusion, aphasia, or global encephalopathy). Management of these symptoms may require steroids, interleukin-6 receptor blockade (tocilizumab), vasopressors, and/or supportive therapy delivered in the intensive care unit. Importantly, we observed in our first five patients[17] and later confirmed in the first 16 patients[19] that the likelihood of developing sCRS is tightly correlated with tumor burden, thus providing a simple means to anticipate patients who are at risk of developing sCRS. This has proven true in pediatric patients.[18,20,21,23] In a study of 33 adult patients who all had high tumor burden, sCRS requiring vasopressors or mechanical ventilation for hypoxia occurred in 7 patients and was effectively managed with IL-6R inhibitor and/or corticosteroid therapy. Other approaches to treat or prevent sCRS are reviewed elsewhere.[23-25]

PERSPECTIVE

The past 2 decades have seen the creation of a new toolbox of recombinant receptors for cancer immunotherapy. Second generation CARs have transformed the adoptive T-cell therapy field. CD19 has become the poster child for CAR therapies. The most remarkable results have been reported to date in ALL, in both adults and children. Remarkably, the CR rate remains high irrespective of patients' age or prior treatments. sCRS may occur in patients with high tumor burden, but means to control it are available. CD19-negative relapse may occur (possibly more commonly in children), for which CD22 CAR therapy may provide an effective recourse.[26] CD19 CARs, which received breakthrough designation by the U.S. Food and Drug Administration at CHOP and at MSKCC in 2014, will soon become part of the armamentarium for B cell-ALL and other B cell malignancies.

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LEUKEMIA, MYELODYSPLASIA, AND TRANSPLANTATION

Management of Hematologic Malignancies in Older Adults

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New Targeted Therapies for Indolent B-Cell Malignancies in Older Patients

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OVERVIEW

Molecularly targeted agents have become an established component of the treatment of indolent B-cell malignancies (iNHL). iNHL disproportionately affects older adults, so treatments that have excellent tolerability and efficacy across multiple lines of therapy are in demand. The numbers and classes of targeted therapies for iNHL have proliferated rapidly in recent years; classes of agents that show promise for older patients with iNHL include anti-CD20 antibodies, phosphatidyl-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway inhibitors, immunomodulators, proteasome inhibitors, epigenetic modulators, and immunotherapies. Here, we review the proposed mechanisms of action, efficacy, and tolerability of novel agents for iNHL, with an emphasis on their applicability to older patients.

For slightly more than a decade, targeted therapies have established a track record of improving outcomes for older patients with lymphoma. Rituximab was the first widely utilized targeted therapy for B-cell lymphomas and resulted in survival improvement when combined with standard chemotherapy for older patients with diffuse large B-cell lymphoma,[1] chronic lymphocytic leukemia (CLL),[2] and follicular lymphoma (FL).[3-6] The addition of rituximab to traditional chemotherapy ushered in a new standard of care for fit patients with both aggressive and indolent B-cell non-Hodgkin lymphomas, termed chemoimmunotherapy, that led to new benchmarks for response rate (RR) and overall survival. In recent years, targeted therapy options have multiplied rapidly, which may once again lead to new standards of care and treatment expectations for B-cell malignancies, in particular indolent lymphomas.[7,8]

Based on 2008 World Health Organization classifications, iNHL comprises the following histologic subtypes: FL; small lymphocytic lymphoma (SLL)/CLL; lymphoplasmacytic lymphoma (LPL), which is defined as Waldenström macroglobulinemia (WM) when associated with a monoclonal immunoglobulin M component and bone marrow involvement; and marginal-zone lymphoma (MZL), which includes marginal-zone lymphoma of mucosa-associated lymphoid tissue.[9] iNHL disproportionately affects older populations (Table 1) and may require multiple treatment courses over decades,[10-12] so there is a need for effective targeted agents as either supplements to or replacements for traditional regimens. An observational study of 1,495 patients with CLL demonstrated that older age was associated with worse performance status, a higher comorbidity score, and more advanced disease at treatment initiation,[13] highlighting the need for agents that have efficacy and tolerability in older patients. Furthermore, age-related host factors reduce treatment tolerability and increase the risk of grade 3 to 5 toxicities,[14] making adverse effects key considerations.

Both the classes and numbers of targeted therapies have rapidly proliferated, resulting in an evolving and more complex treatment landscape. Available classes that have spawned second-generation agents include monoclonal antibodies, cell-signaling pathway inhibitors, immunomodulators, and proteasome inhibitors. Several new classes of agents are in clinical trials and show promise (Table 2). We will discuss these classes of agents, their proposed mechanisms of action, and the clinical data regarding their efficacy and tolerability in older patients. Our emphasis will be on those that are currently marketed, have been studied in older populations, and have later-phase clinical data.

ANTI-CD20 ANTIBODIES

CD20 is a glycosylated phosphoprotein antigen found on the surface of B lymphocytes at most stages of B-cell development, starting at the pro-B-cell phase but ending before differentiation into plasma cells. Its function is believed to be optimization of antibody responses, but it has no known natural ligand.[15,16] Monoclonal antibodies directed against CD20 neutralize both benign and malignant B cells; anti-CD20 antibody cytotoxicity mechanisms include antibody-dependent cell-mediated cytotoxicity (ADCC), complement-

TABLE 1. Median Ages of Presentation of iNHL Subtypes

Disease	Median Age (Years)	Reference(s)
CLL/SLL	72	12
LPL	60-64	10, 11
MZL	72	12
FL	65	12

Abbreviations: iNHL, indolent B-cell malignancies; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; LPL, lymphoplasmacytic lymphoma; MZL, marginal-zone lymphoma; FL, follicular lymphoma.

dependent cytotoxicity, and apoptosis.[17,18] With the advent of rituximab, anti-CD20 monoclonal antibody therapy assumed an essential role in the therapy of the majority of B-cell malignancies. Novel anti-CD20 agents have been developed in an effort to build on the progress made in the rituximab era. There are two recognized classes of anti-CD20 antibodies: type 1 (ibritumomab, rituximab, and ofatumumab) and type 2 (obinutuzumab). Type 1 antibodies organize CD20 molecules into "rafts" and exert their effects primarily by ADCC and complement-dependent cytotoxicity, and less so by apoptosis. Type 2 antibodies utilize apoptosis to a greater degree and also exert more potent ADCC as well.[19,20]

The radioimmunoconjugate [90]yttrium-ibritumomab-tiuxetan (YIT) fuses a murine anti-CD20 antibody to a chelator (tiuxetan) that holds the beta-emitter isotope 90Y. YIT received initial approval in 2002 for relapsed or refractory low-grade lymphoma, but recent data show that it has considerable single-agent efficacy as initial therapy[21,22] or consolidation therapy[23] for patients with FL or MZL. The percentage of patients age 60 or older ranged from 28% to 50% in those stud-

KEY POINTS

- Older patients are more prone to comorbidities, reduced performance status, and grade 3 or higher toxicities, making safety and tolerability key considerations in the choice of treatment for indolent B-cell malignancies.
- New anti-CD20 monoclonal antibodies, administered in combination with chlorambucil, have demonstrated efficacy in patients with chronic lymphocytic leukemia who are older or have comorbidities.
- The phosphatidyl-3-kinase inhibitor idelalisib and the Bruton's tyrosine kinase inhibitor ibrutinib have demonstrated good efficacy and tolerability in patients with chronic lymphocytic leukemia, including patients with high-risk cytogenetics.
- mTOR inhibitors, immunomodulatory drugs, and proteasome inhibitors have efficacy across several indolent B-cell malignancy histologies but have not resulted in high tolerability in all patient subtypes.
- Immunotherapies such as programmed cell death 1 blockade show promise of efficacy with excellent tolerability.

ies, with minimal or no grade 3 to 4 nonhematologic adverse events. In the randomized consolidation FIT trial, 8% of patients in the YIT arm experienced grade 3 to 4 infections versus 2% of patients in the control arm. Thus, radioimmunoconjugate therapy offers potent single-agent efficacy coupled with excellent tolerability, a favorable combination in older patients.

Ofatumumab was approved by the U.S. Food and Drug Administration (FDA) in October 2009 as a single agent for relapsed CLL after a single-arm, phase II study with 59 patients of median age 64 with relapsed or refractory disease after fludarabine and alemtuzumab therapy demonstrated a 58% overall response rate (ORR). In the trial, 27 patients were age 65 or older and 10 patients were age 70 or older. Response rates were similar for younger and older patients. Grade 3 to 4 infections developed in 12% of patients, 10% of patients experienced fatal infections, and 64% of patients experienced infusion reactions.[24]

A subsequent open-label trial in the first-line setting, COMPLEMENT-1, randomly assigned 447 patients who were not candidates for fludarabine-based therapy to receive ofatumumab and chlorambucil (217 patients) versus chlorambucil alone (227 patients). The median age was 69, with 69% of patients age 65 or older, and 72% of patients had at least two comorbidities including chronic kidney disease; thus, the trial had excellent applicability to patients with advanced age. Efficacy and safety results are summarized in Table 3. Briefly, first-line ofatumumab and chlorambucil achieved a higher RR and improved progression-free survival (PFS) compared with chlorambucil alone.[25] It should be noted that the comparator arm, chlorambucil monotherapy, is commonly reserved for patients who are candidates for minimally aggressive therapy, yet still produced substantial rates of adverse events and severe infections. A Canadian cost-effectiveness analysis of the COMPLEMENT-1 trial demonstrated an incremental cost-effectiveness ratio of CAD $68,672 per quality-adjusted life-year (QALY) gained.[26] On April 17, 2014, the results from COMPLEMENT-1 led to the FDA approval of ofatumumab in combination with chlorambucil for the front-line treatment of patients with CLL.

Obinutuzumab received FDA approval on November 1, 2013, for the first-line treatment of patients with CLL in combination with chlorambucil, based on results of the open-label, phase III CLL11 trial of 781 patients comparing obinutuzumab and chlorambucil, rituximab and chlorambucil, and chlorambucil alone. All patients had coexisting morbidities and a median age of 73. Results are summarized in Table 3. The obinutuzumab-chlorambucil arm demonstrated superior PFS, and overall survival favored obinutuzumab/chlorambucil over chlorambucil alone (RR 0.41; p = 0.002), but did not reach statistical significance for obinutuzumab/chlorambucil compared with rituximab/chlorambucil. In the aggregate, hematologic toxicity was higher in the obinutuzumab/chlorambucil arm versus rituximab/chlorambucil, emphasizing that the improved PFS was somewhat counterbalanced by increased toxicity. Of note, 109 of 240 patients in the obinutuzumab plus chlorambucil

TABLE 2. Selected Molecular Pathways and Marketed Novel iNHL Therapies That Target Them

Pathway	Molecular Target	Agent	Dosing	Disease(s)	FDA Indication(s)	Phase(s) of Clinical Trial Data
CD20	CD20	Ofatumumab	300 mg IV day 1 and 1,000 mg IV day 8 (cycle 1) and 1,000 mg IV day 1 (cycles 2-12) of 21-day cycles	CLL, FL	CLL (first-line, relapsed)	II, III
		Obinutuzumab	100 mg IV on day 1, 900 mg IV on day 2, and 1,000 mg IV on days 8 and 15 (cycle 1) and 1,000 mg on day 1 (cycles 2-6) of 21-day cycles	CLL	CLL (first-line)	III
		Ibritumomab tiuxetan	14.8 MBq/kg IV once, maximum 32 mCi	FL, MZL	iNHL or FL (relapsed); FL (first-line consolidation)	II, III
PI3K/Akt/mTOR	PI3K	Idelalisib	150 mg PO BID	CLL, FL, LPL, MZL	CLL/SLL, FL (relapsed)	II, III
	mTOR complex 1	Everolimus	10 mg PO QD	CLL, MZL, WM	Renal cell carcinoma, breast cancer	II
		Temsirolimus	25 mg IV every week	CLL, FL, WM	Renal cell carcinoma	II
	BTK	Ibrutinib	420 mg PO QD	CLL/SLL	MCL (relapsed), CLL (relapsed and del[17p]), WM	II, III
			560 mg PO QD	FL		
			420 mg PO QD	WM		
Immunomodulation	Cereblon	Lenalidomide	25 mg PO QD, days 1-21 of 28-day cycles	FL, MZL, SLL, WM	Multiple myeloma, MCL, MDS	II
Proteasome	20S subunit chymotryptic site	Bortezomib	1.6 mg/m^2 IV on days 1, 8, 15, and 22 of 35-day cycles	CLL, SLL, FL, MZL, WM	Multiple myeloma, MCL (relapsed)	I, II, III
		Carfilzomib	20 mg/m^2 IV on days 1, 2, 8, and 9 (cycle 1), 36 mg/m^2 IV (cycle 2-6), 20 mg/m^2 on days 1 and 2 (maintenance) of 21-day cycles	CLL/SLL, FL, WM	Multiple myeloma (relapsed)	I, II
Epigenetics	Histone deacetylase	Vorinostat	200 mg PO BID days 1-14 of 21-day cycles	FL, MZL	Cutaneous T cell lymphoma	I, II
	DNA methyltransferase	5-azacitidine	75 mg/m^2 SC on days 1-7 every 3 to 8 weeks	CLL	MDS	II
		Decitabine	15 mg/m^2 IV on days 1-5 of a 28-day cycle	CLL	MDS	I
Immunotherapy	PD-1	Nivolumab	3 mg/kg IV day 1 of 14-day cycles	FL	melanoma	I, II

Abbreviations: IV, intravenous; CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; PO, by mouth; SC, subcutaneous; Bq, becquerels; QD, once daily; BID, twice daily; MZL, marginal-zone lymphoma; LPL, lymphoplasmacytic lymphoma; WM, Waldenström macroglobulinemia; SLL, small lymphocytic lymphoma; MCL, mantle cell lymphoma; MDS, myelodysplastic syndrome.

arm were older than age 75. Of those patients, 45% experienced serious adverse events, and 5% of patients experienced adverse events that led to death; similar rates were seen in the comparator arms.[27] It is interesting to note that the CLL11 and COMPLEMENT-1 trials used different chlorambucil regimens. A 65-kg person with body-surface area 1.8 m^2 would have received a substantially higher dose of chlorambucil per cycle (126 vs. 65 mg) if enrolled in the COMPLEMENT-1 trial, possibly accounting for the lower response rate and PFS observed for the chlorambucil arm of the CLL11 trial.

A cost-effectiveness study of obinutuzumab versus rituximab in combination with chlorambucil found that obinutuzumab increased QALYs by 0.56 compared with rituximab, with an 89% probability that obinutuzumab was cost-effective at the $100,000 threshold.[28] The study was based on Medicare reimbursements and wholesale acquisition costs and was sponsored by Genentech, which markets obinutuzumab. In contrast, the United Kingdom's National Institute for Health and Clinical Excellence (NICE) found that obinutuzumab/chlorambucil versus rituximab/chlorambucil added $45,000 per QALY in costs and $77,130 versus bendamustine/rituximab in costs. NICE initially decided not to fund obinutuzumab, finding it inadequately cost effective.[29,30] NICE revised its decision, funding obinutuzumab for the first-line treatment of patients with CLL after a nondisclosed discounted price was offered by the company.[31]

Ofatumumab and obinutuzumab demonstrated substantial activity in untreated older individuals, except for patients with a 17p deletion (del[17p]). The caveats from these studies

TABLE 3. Selected Randomized Controlled Trial Data for Chemoimmunotherapy in Untreated CLL with Novel Anti-CD20 Monoclonal Antibodies

Study, Reference	Regimen	Median Age (Years)	ORR (%)	PFS (Months)	Grade 3 or Higher Toxicity (%)	Infusion Reaction (Grade 3 or Higher, %)	Infection (Grade 3 or Higher, %)	Death (%)
COMPLEMENT-1, Hillmen et al 2013[25]	Ofatumumab and chlorambucil	69	82	22.4	50	10	15	2
	Chlorambucil	70	69	13.1	43	n/a	14	2
CLL11, Goede et al 2014[27]	Obinutuzumab and chlorambucil	74	77	26.7	73	21	11	4
	Rituximab and chlorambucil	73	66	16.3	56	4	13	6
	Chlorambucil	72	31	11.1	50	n/a	14	9

are that infusion reactions and infections are encountered frequently. In older patients, managing infusion reactions, as a result of effects of premedications, may be more challenging. Severe infections may also be more difficult for older populations because of reduced organ reserves but are likely to be encountered regardless of the regimen chosen.

PI3K/AKT/MTOR PATHWAY ANTAGONISTS

The PI3K/Akt/mTOR signaling pathway governs a wide range of cellular housekeeping and growth functions. The multiple classes and isoforms of PI3K enzymes transduce signals from receptor tyrosine kinases at the cell membrane, notably including the B-cell receptor (BCR), and activate the serine-threonine kinase Akt, which functions as an oncogenic effector. Akt in turn indirectly activates mTOR kinase complexes 1 and 2. Bruton's tyrosine kinase (BTK) is also a downstream target of PI3K signaling, an activator of Akt, and a crucial factor in BCR signaling and B-cell development.[32-34]

Preexisting and new therapeutic agents that target various steps of the PI3K/Akt/mTOR pathway have demonstrated efficacy in B-cell lymphomas and have obtained FDA approvals for the treatment of patients with iNHL. The oral PI3K-delta inhibitor idelalisib, which interferes with BCR signaling and microenvironmental support signals in both healthy and malignant B cells, received FDA approval in July 2014, based on clinical trial data that demonstrated single-agent efficacy in relapsed iNHL and, in combination with rituximab, activity in relapsed CLL. In a phase II study of 125 heavily pretreated patients of median age 64 with iNHL whose disease was refractory to both rituximab and alkylating agents (FL, 72 patients; SLL, 28 patients; MZL, 15 patients; and LPL, 10 patients), treatment with idelalisib resulted in a 57% RR, with PFS of 11 months. Hematologic serious adverse events included neutropenia (27%), anemia (2%), and thrombocytopenia (6%); nonhematologic serious adverse events included transaminase elevations (13%), diarrhea (13%), and pneumonia (7%). In total, 54% of patients experienced serious adverse events, and 20% of patients discontinued therapy because of adverse events.[35]

In a double-blinded, placebo-controlled, phase III study, 220 pretreated patients of median age 71 with CLL were randomly assigned to receive idelalisib and rituximab or placebo and rituximab. Treatment with idelalisib significantly im-

proved PFS, the primary endpoint (hazard ratio [HR], 0.15; $p < 0.0001$). ORR improved from 13% to 81%, and the 12-month OS was 92% in the idelalisib/rituximab arm compared with 80% in the placebo/rituximab arm (HR, 0.28; $p = 0.02$). Notably, 42% of patients in the idelalisib arm had a del(17p); idelalisib showed efficacy across all prognostic subgroups. Severe adverse events occurred in 40% of the patients in the idelalisib arm compared with 35% of the patients in the placebo arm. Grade 3 or higher hematologic adverse events were similar between the two arms. Discontinuation of the study drug occurred in 8% of patients taking idelalisib and in 10% of patients in the placebo group.[36] Idelalisib appears to have excellent efficacy in pretreated patients with iNHL with manageable toxicity. The placebo-controlled, randomized CLL trial adds perspective to the tolerability data seen in the single-arm trial; the relatively high discontinuation rate may be more attributable to the age and pretreatment status of the patient populations enrolled, as evidenced by the 10% placebo group discontinuation rate in the randomized study.

Next-generation PI3K inhibitors are also in development, including duvelisib (IPI-145), a PI3K-delta and PI3K-gamma inhibitor. Duvelisib has demonstrated efficacy in early phase studies of patients with FL, MZL, LPL,[37] and CLL.[38] It was well tolerated and did not have a decrease in efficacy in adverse-risk CLL.

The rapamycin (sirolimus) analogs temsirolimus and everolimus inhibit mTOR complex 1, with the effects of stimulating apoptosis and inhibiting cell growth and proliferation.[33,39] Those second generation "rapalogs" have demonstrated efficacy in both aggressive and iNHL, as explored in several phase II trials.[33,40-43] Trial results are summarized in Table 4. The limited available clinical data for those agents suggest that they may be less tolerated than other agents indicated for iNHL, which may limit their use in older patients. Temsirolimus and everolimus have not yet been FDA-approved for the treatment of patients with iNHL. Interestingly, mTOR inhibition may help overcome resistance by a mobilizing effect.[43] Inhibition also seems to overcome fludarabine resistance by suppressing mTOR complex 1–mediated metabolic reprogramming, manifested by higher rates of glycolysis and oxidative phosphorylation, in CLL cells.[44]

Ibrutinib, a covalent, irreversible, oral inhibitor of BTK, received FDA approval in February 2014 for the treatment of patients with CLL. In July 2014, the label was extended to

TABLE 4. Selected Phase II Trial Data for mTOR Inhibition in iNHL

Regimen	Disease Subtype(s)	Median Age (Years)	Overall Response Rate (%)	Progression-Free Survival (Months)	Grade 3 or Higher Toxicity (%)	Treatment-Related Deaths (%)	Toxic Discontinuation (%)	Reference
Everolimus	MZL	71	25	14	-	4	42	40
Everolimus	WM	63	50	21	67	0	10	41
Everolimus	CLL	74	18	5.1	68 hematologic, 41 nonhematologic	9	14	43
Temsirolimus	FL	59	54	12.7	-	1	18	42
	CLL, WM	57	11	4.6				

Abbreviations: MZL, marginal-zone lymphoma; WM, Waldenström macroglobulinemia; CLL, chronic lymphocytic leukemia; FL, follicular lymphoma.

patients with the del(17p) cytogenetic abnormality. A phase Ib/II, multicenter trial of ibrutinib was conducted in 85 patients with relapsed CLL; the median age was 66, and 35% of patients were age 70 or older. Patients had received a median of four prior therapies, and 33% of patients harbored the del(17p). In the study, 71% of patients responded to therapy and 18% of patients had a partial response (PR) with lymphocytosis. Patients with a del(17p) experienced a 68% ORR. The discontinuation rate was 4% in the 420-mg cohort and 12% in the 840-mg cohort. The most common severe adverse events were pneumonia (12%) and dehydration (6%). Serious bleeding occurred in 5% of patients and death occurred in 8% of patients. Considering the age and prognostic features of the study population, ibrutinib was well tolerated with no decrease in efficacy for patients with a del(17p).[45]

Ibrutinib was also studied as first-line therapy in a phase Ib/II trial of 31 patients with CLL/SLL age 65 or older; the median age was 71. The ORR was 71%, with a 13% complete response (CR) rate. Toxicity was mainly grade 1 to 2 in severity, with serious adverse events including diarrhea (13%), fatigue (3%), and infection (10%). Neither grade 4 nor grade 5 infections were reported.[46] Thus, in the first-line setting among older patients, ibrutinib is an efficacious, well-tolerated option.

Ibrutinib has also been studied versus ofatumumab in relapsed or refractory CLL/SLL in a multicenter, open-label, phase III trial that enrolled 391 patients; the median age was 67, and 32% of patients had a del(17p). The primary endpoint was PFS. Compared with ofatumumab, ibrutinib had superior PFS (HR, for progression 0.22; p < 0.001), OS (HR, 0.43; p = 0.005), and ORR (63% versus 4%; p < 0.001). Ibrutinib also demonstrated superior efficacy for patients with del(17p). Severe adverse events occurred in 57% of patients who received ibrutinib and 47% of patients who received ofatumumab. Bleeding events occurred more in the ibrutinib group (44%) compared with the ofatumumab group (12%). Grade 3 or higher infections occurred in 24% of patients in the ibrutinib arm and in 22% of patients in the ofatumumab arm. Discontinuation because of adverse events occurred in 4% of patients in each group. Fatal adverse events occurred in 4% and 5% of patients in the ibrutinib and ofatumumab arms, respectively. The relatively low rate of response to ofatumumab compared with the study that resulted in the initial FDA approval may have been attributable to more rigorous re-

quirements for serial CT scanning to assess response.[47] The efficacy of ibrutinib (versus placebo) is also being studied in combination with bendamustine and rituximab in refractory and relapsed CLL; the phase III HELIOS trial is currently ongoing.[48]

Ibrutinib has also shown efficacy in relapsed or refractory WM. In a phase II study of 63 patients of median age 63 who had received a median of two prior therapies, ibrutinib induced PRs in 57% of patients and minor responses in 24% of patients. Treatment was discontinued by 6% of patients. Common grade 2 or higher toxicities included thrombocytopenia (14%) and neutropenia (19%).[49] On January 29, 2015, the FDA approved ibrutinib for treatment of WM. In FL, a phase II study of ibrutinib in 38 evaluable patients of median age 64, demonstrated a more modest 30% ORR in the ibrutinib arm, but 65% of patients had tumor size reduction. Grade 3 to 4 events occurred in 30% of patients, and 5% of patients discontinued treatment because of adverse events. There was one death due to gastric hemorrhage.[50]

Ibrutinib has developed a track record as an efficacious and well-tolerated agent in CLL, especially in older patients. The potential for bleeding in patients treated with ibrutinib and the exclusion of patients on warfarin from most clinical trials suggest that ibrutinib should be avoided in anticoagulated patients or those patients with a history of serious bleeding (such as intracranial hemorrhage). Importantly, it also offers efficacy for patients without regard to cytogenetic risk. Ibrutinib has shown efficacy in mantle cell and diffuse large cell histologies as well. Later-generation BTK inhibitors are also in development.[51,52]

IMMUNOMODULATORY AGENTS

The immunomodulatory drugs (IMiDs) are thalidomide analogs that have the capacity to alter immune microenvironments, have antiangiogenic effects, promote T-cell costimulation, and activate NK cells.[53] Lenalidomide has been shown to stimulate T-cell– and NK-cell–mediated cytotoxicity in indolent lymphomas.[54] Molecularly, IMiDs interfere with the function of the ubiquitin ligase cereblon (CRBN), which may be the key mediator for their microenvironmental and immunomodulatory effects. CRBN has been shown to interact with potassium and chloride channels, AMP-

activated protein kinase, and Cullin 4 to function as part of an E3 ubiquitin ligase complex.[55] CRBN is required for the therapeutic effect of IMiDs. Its downstream signaling targets include interferon regulatory factor 4 and tumor necrosis factor-alpha.[56] Lenalidomide-bound cereblon, in its ubiquitin ligase function, also targets the Ikaros family zinc finger proteins 1 and 3, which are B-cell–specific transcription factors, for degradation.[57]

Lenalidomide has shown efficacy in the treatment of relapsed or refractory iNHL. In a study of 43 patients of median age 63 (21% older than 75) with FL, SLL, or MZL, 25 mg lenalidomide monotherapy administered 3 out of 4 weeks for up to 52 weeks induced a 23% ORR with a median duration of response of 16.5 months or greater.[58] Common adverse events (any grade) included neutropenia (58%), fatigue (51%), thrombocytopenia (42%), anemia (37%), and diarrhea (33%). Common grade 3 to 4 toxicities included neutropenia (46%), thrombocytopenia (19%), anemia (9%), asthenia (5%), and pneumonia (5%); 67% of patients required dose reductions or interruptions. Treatment discontinuation because of adverse events occurred in 19% of patients; there was one treatment-related death. Lenalidomide showed efficacy in a relatively heavily pretreated population (median of three prior treatments) with moderate tolerability, with a study population that included older patients.

Later-line efficacy of lenalidomide led to a first-line, phase II trial of lenalidomide and rituximab in 110 patients with iNHL. Histologic subtypes included FL (50 patients), SLL (30 patients), and MZL (30 patients), with median ages of 56, 59, and 59, respectively. Treatment with lenalidomide plus rituximab resulted in an ORR of 90%, a 65% CR rate, and a median PFS of 54 months. Response rates were similar across subtypes but highest in patients with FL. The most common grade 3 to 4 AEs included neutropenia (35%), pain or myalgia (9%), rash (7%), fatigue (5%), thrombosis (5%), and pulmonary symptoms (5%); 28% of patients required dose reductions. No treatment-related deaths occurred.[59] Thus, the combination of lenalidomide and rituximab was well tolerated with good efficacy, though the median patient ages were younger than those typically seen for the histologic subtypes treated. Toxicity and dose-reduction or discontinuation rates may be higher in older patient populations. This approach is under investigation in a phase III trial that recently completed accrual to evaluate rituximab and lenalidomide versus rituximab and chemotherapy in untreated patients with FL.

IMiDs have also demonstrated efficacy in WM.[60] The combination of rituximab and lenalidomide induced a 50% ORR in a trial of 16 patients; 12 had been previously untreated and four patients had received prior therapy. The median age was 65. However, 13 out of 16 patients experienced a hematocrit decrease, resulting in early termination of enrollment; 88% of patients required treatment discontinuation. The most common grade 3 to 4 toxicity was neutropenia (31%).[61] Given the concern for thalidomide and neuropathy in WM patients, and the unique, idiosyncratic association of lenalidomide with anemia

in WM, IMiD therapy will require further development before being ready for "prime time" in WM, especially in older patients who may be more affected by adverse events.

PROTEASOME INHIBITORS

Proteasome inhibitors such as bortezomib and carfilzomib inhibit the chymotrypsin-like sites of the proteasome's 20S subunit. That inhibition disrupts protein homeostasis and protein folding quality control, resulting in proteotoxic stress and activation of the unfolded protein response, leading to cell death; cancer cells experience higher toxicity as they are more susceptible to proteotoxic stress.[62] Bortezomib has been in use for the treatment of multiple myeloma for more than a decade, and its use in mantle cell NHL dates back several years, having received approval for relapsed or refractory disease in 2006 and approval for first-line therapy in October 2014. Bortezomib is still being studied for use in indolent lymphoma.

Three phase II studies have established efficacy of bortezomib in relapsed or refractory iNHL.[63-65] Results varied, with response rates ranging from 13% to 53%; the study with the lowest ORR was notable for a 64% stable disease rate.[64] None of the studies reported grade 3 neuropathy higher than 10%. Notably, Di Bella et al enrolled a cohort of median age 70,[64] with grade 3 or 4 adverse events including thrombocytopenia (20%), fatigue (10%), neutropenia (8.5%), neuropathy (6.8%), and diarrhea (6.8%).[64] Thus, bortezomib may be a reasonably well-tolerated option with modest efficacy in an older population. de Vos et al compared biweekly (1.3 mg/m^2 on days 1, 4, 8, and 11 of 21-day cycles) with weekly (1.6 mg/m^2 on days 1, 8, 15, and 22 of 35-day cycles) bortezomib in combination with rituximab and found the weekly regimen to be better tolerated, with fewer grade 3 or higher adverse events, including neuropathy (10% biweekly versus 5% weekly).[65]

These initial favorable results led to a randomized, phase III trial of bortezomib plus rituximab versus rituximab alone for patients with relapsed or refractory FL. In the study, 1.6 mg/m^2 of bortezomib was administered intravenously on days 1, 8, 15, and 22 of 35-day cycles. A total of 676 patients were enrolled with a median age of 57; 28% of patients were older than age 65. The addition of bortezomib resulted in a modest increase of PFS from 11 to 13 months. Grade 3 or higher adverse events were higher in the combination arm, 46% compared with 21%. Grade 3 or higher infection (11% vs. 4%), neutropenia (11% vs. 4%), diarrhea (7% vs. 0%), and neuropathy (3% vs. 1%) favored rituximab alone. The combination arm experienced 1% possible treatment-related deaths.[66] Given the higher toxicity of the combination regimen, the modest 2-month improvement in PFS was disappointing.

However, recent data in high-tumor burden iNHL suggest that combination therapy with bortezomib and rituximab may still be desirable. A front-line phase II trial with 42 patients of median age 61 with primarily FL received 1.6 mg/m^2 of bortezomib intravenously on days 1, 8, 15, and 22 of 35-day cycles. The ORR was 70% with a CR rate of

TABLE 5. Early-Phase Data for Selected Miscellaneous Investigational (Nonmarketed) Agents for iNHL Under Preliminary Testing

Agent	Molecular Target/Pathway	Disease(s)	Notable Outcomes	Reference(s)
ABT-199	BCL-2	FL, MZL	73% RR in FL	81
CAR T cells	Multiple, primarily CD19	CLL, FL	CRs, PRs; very limited data	77-80
Panobinostat (with everolimus)	HDAC	FL, CLL	33% RR, high toxicity	71
Pidilizumab	PD-1	FL	66% ORR, no grade 3 or higher toxicity	82
Polatuzumab vedotin	ADC: CD79b (BCR) and mitotic function	FL	67% ORR as single-agent	75
SAR3419	ADC: CD19 and mitotic function	FL	29% ORR, 43% SD	74
TRU-016 (with bendamustine and rituximab)	SMIP: CD37	FL, SLL	83% ORR	76

Abbreviations: FL, follicular lymphoma; MZL, marginal-zone lymphoma; RR, response rate; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; PR, partial response; HDAC, histone deacetylase; ORR, overall response rate; ADC, antibody-drug conjugate; SD, stable disease; SMIP, monospecific protein therapeutic; SLL, small lymphocytic lymphoma.

40%. The discontinuation rate was 7%, with grade 1 to 2 neuropathy experienced by 16% of patients. There was no grade 3 or higher neuropathy. Other grade 3 to 4 adverse events included neutropenia (5%), fever (5%), and infection (5%).[67] Bortezomib and rituximab represent a potentially efficacious therapy combination. Extrapolating from the multiple myeloma literature, subcutaneous bortezomib administration may reduce nonhematologic toxicity without compromising efficacy, a key consideration for older patients.

Bortezomib has not yet been FDA-approved for iNHL, although in WM bortezomib is a standard agent in both frontline and relapsed settings; that topic has been reviewed elsewhere.[60] The second-generation proteasome inhibitor carfilzomib has been utilized as a neuropathy-sparing approach in WM. A phase II study of 31 patients of median age 61 evaluated carfilzomib, rituximab, and dexamethasone, which led to an 87% ORR. Grade 3 or higher toxicities included hyperglycemia (23%), hyperlipasemia (16%), neutropenia (10%), and cardiomyopathy (3%). There was no grade 3 or 4 neuropathy.[68] Carfilzomib may also have activity against other histologies in the relapsed or refractory setting: a phase I trial of carfilzomib included six patients with FL and one patient with CLL/SLL; carfilzomib treatment resulted in stable disease in four of the patients with FL and the patient with CLL/SLL.[69]

FUTURE DIRECTIONS: OTHER AGENTS

Additional classes of agents have shown promise in treating iNHL, including histone deacetylase inhibitors,[70,71] hypomethylating agents,[72,73] antibody-drug conjugates (ADCs),[74,75] monospecific protein therapeutics[76]; chimeric antigen receptor T cells directed against CD19,[77-80] BCL-2 inhibitors,[81] and programmed cell death (PD)-1 T cell inhibitory receptor antibodies[82,83] (Table 5). Among these, histone deacetylase inhibitors, ADCs, and PD-1 antagonists have potential for excellent tolerability in older patients and might prove highly useful in early-line combination regimens or as later-line single agents for patients with advanced age or extensive comorbidities. Hopefully, further trials that emphasize older patients with the above investigational therapies and recently approved agents will lead to more data that can be used to address one of the largest unmet needs in the treatment of indolent hematologic malignancies: providing well-tolerated drugs across multiple lines of therapy for older patients.

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Hematopoietic Cell Transplantation for Myelodysplastic Syndrome

H. Joachim Deeg, MD

OVERVIEW

Although high-dose chemotherapy may cure a small subset of patients with myelodysplastic syndrome (MDS), allogeneic hematopoietic cell transplantation (HCT) is the only currently available modality that is curative in a large proportion of patients. Approximately 30% to 40% of patients with high-risk MDS and 60% to 80% of patients with low-risk MDS survive long-term in remission. Disease classification and risk assessment schemes, such as the World Health Organization (WHO) Prognostic Scoring System (WPSS), the Revised International Prognostic Scoring System (IPSS-R), and patient characteristics as assessed by the HCT Comorbidity Index (HCT-CI) or other scores, provide guidance for patient management. First, by defining the prognosis of patients without HCT, these tools help physicians decide who should and who should not be transplanted. Second, they predict at least in part how successful a transplant is likely to be. Pretransplant cytogenetics and marrow myeloblast count are the strongest risk factors for post-transplant relapse. The HCT-CI allows physicians to estimate the probability of nonrelapse mortality after HCT; recent data suggest that there is also a relationship to the development of graft-versus-host disease (GVHD). In general, the emphasis has shifted from high-dose therapy, aimed at maximum tumor-cell kill, to reduced-intensity conditioning (RIC), relying on the donor cell-mediated graft-versus-tumor (GVT) effects to eradicate the disease. GVT effects are most prominent in patients who also develop GVHD, especially chronic GVHD. Thus, ongoing work is directed at reducing GVHD while maintaining potent GVT effects and at exploiting the growing knowledge of somatic mutations for the development of targeted therapies.

Although high-dose chemotherapy may cure a small subset of patients with MDS, allogeneic HCT is currently the only modality shown to be curative for 30% to 80% of patients, depending on patient and disease characteristics, the source of stem cells, and the transplant strategy applied. The availability of human leukocyte antigen (HLA)-matched unrelated donors, HLA-identical siblings, (HLA-nonidentical) cord blood, and HLA-haploidentical relatives allows for the identification of suitable stem cell donors for the vast majority of patients. However, despite considerable progress, problems remain in regards to the prevention of GVHD while maintaining the desired graft-versus-leukemia (GVL) effect—an essential factor in disease eradication and optimization of transplant conditioning regimens.

DISEASE CLASSIFICATION AND TRANSPLANTATION

The WHO classification,[1] evolving from the classic French-American-British (FAB) schema,[2] has identified MDS subcategories, such as del(5q) with superior prognosis or, conversely, refractory cytopenia with multilineage dysplasia with inferior prognosis relative to refractory anemia, and has categorized all patients with 20% or more marrow myeloblasts as having acute myeloid leukemia (AML; Table 1). An additional poor risk factor is the presence of marrow fibrosis.[3] These parameters are important when considering indications for HCT. The incorporation of cytogenetic information and transfusion needs and the degree of peripheral blood cytopenias in risk assessment scores such as the WPSS[4] or the IPSS-R[5] (Table 2 and the inclusion of age, for example, in the MD Anderson score,[6] have refined our prognostic ability and thereby provided guidance for HCT—specifically a more conservative, observing strategy for good risk and a more aggressive, intensive treatment approach for patients with poor-risk disease.

TRANSPLANT RISK ASSESSMENT
Patient Characteristics

Older age has long been considered a contraindication for transplantation. Studies over the past decade have shown that more than chronologic age, comorbid conditions that may be associated with advanced age (but could also be present in younger patients) are the dominant factors that negatively affect transplant outcome. Those conditions have been cataloged in the HCT-CI, and results clearly show inferior outcome with increasing HCT-CI scores, which include prior diagnosis of a solid

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tumor, hypertension, or impaired pulmonary function, among others.[7] Other classification schemes have also included transplant characteristics, in particular, the stem cell source,[8] and more recently have applied a modified system to patients transplanted with reduced-intensity conditioning (RIC) regimens.[9]

Conditioning Regimens

The optimum conditioning regimen has not been determined. In general, however, the emphasis in allogeneic HCT has shifted from high-dose (myeloablative) therapy, aimed at cytotoxic tumor-cell kill, to low (nonmyeloablative) or RIC, relying on immune effects mediated by GVT effects to eradicate the disease.[10-13] RIC regimens have reduced the incidence and severity of treatment-related toxicity and day 100 mortality to less than 10% or even 5% but generally have resulted in a higher incidence of MDS relapse than observed with high-intensity regimens.[14] In fact, a recent multi-institutional U.S. trial involving patients with MDS or AML (BMT CTN 0901) was closed prematurely because of inferior outcome in patients conditioned with RIC regimens.

Donor–Host Immunity

Allogeneic HCT carries the risk of the adverse effects of the bidirectional reactivity of donor and host cells. Host-versus-donor reactivity leading to rejection of the graft is an infrequent event. Donor-versus-host reactivity leading to clinical manifestations, however, occurs in about half of all patients.[15,16] Although GVT effects contribute to disease eradication, those effects are most prominent in patients who also show clinical evidence of GVHD. In fact, the most prominent GVL effects are observed in patients who develop chronic GVHD, which occurs in 40% to 60% of patients transplanted with unmanipulated donor cells[17]; the incidence tends to be lower in patients receiving T cell–depleted grafts[18] and, possibly, patients administered post-transplant cyclophosphamide,[19] which appears to be capable of inactivating host-reactive donor cells.

KEY POINTS

- Hematopoietic cell transplantation provides curative therapy for patients with myelodysplastic syndrome.
- The clonal karyotype is the strongest predictor of post-transplant relapse.
- The availability of human leukocyte antigen (HLA)-matched related and unrelated donors, HLA-haploidentical relatives, and umbilical cord blood helps identify donors for the vast majority of patients.
- Additional research is needed to prevent graft-versus-host disease while maintaining the graft-versus-tumor effect.
- As myelodysplastic syndrome is primarily a disease of older age and quality of life is a top priority for most older individuals, discussions regarding transplantation in older patients must include not only the acute effects of transplantation but also delayed effects.

Further, immune-incompetence early after HCT and GVHD-associated immunosuppression severely increases the risk of systemic infections—another cause of post-HCT morbidity and mortality.[20]

Stem Cell Source

Peripheral blood progenitor cells are currently the preferred source of stem cells, because of their rapid kinetics of engraftment and more potent GVL effect than marrow cells, albeit at the risk of a higher incidence of GVHD.[15] Cord blood cells are typically associated with slow engraftment and the associated risk of bleeding and infections.[21,22] The incidence of relapse, however, in many studies has been lower than with stem cells obtained from adult donors. Transplantation of HLA-haploidentical cells carries an increased risk of graft rejection, although recently used conditioning regimens have reduced that risk, and the incidence of GVHD has been similar to or lower than that observed with HLA-matched donor cells, presumably related to the post-transplant administration of cyclophosphamide.[23] Data from patients with MDS are too limited to draw firm conclusions regarding the effect on relapse.

TRANSPLANT INDICATIONS AND OUTCOME

Based on several retrospective and decision analyses, HCT is typically offered to patients with intermediate-2 or high-risk disease (by IPSS criteria) or (intermediate) poor- and very poor–risk by IPSS-R (or similarly by WPSS) criteria, whereas patients in lower-risk categories are often managed more conservatively, for example, with hypomethylating agents, since significant advantages of HCT in regard to duration of survival have been shown only in those patients at higher risk.[24-26] Nevertheless, there is a tendency to offer HCT also for lower-risk disease, particularly for younger patients.[12,27] Not unexpectedly, long-term survival in remission (following HCT from HLA-matched related or unrelated donors and high-intensity conditioning) is in the range of 75% for patients with low-risk disease, approximately 60% with intermediate-1, 45% with intermediate-2, and 30% for patients with high-risk MDS.[27,28] The major factors with a negative effect on relapse-free survival are pre-HCT karyotype and marrow blast count. Patients with very poor cytogenetics, including monosomal karyotype, have a 10% or less probability of long-term survival.[27,29]

Caution is indicated when advising patients who are considered transplant candidates to undergo a trial with hypomethylating agents. Clearly, a proportion of patients (approximately 45%) will respond to hypomethylating therapy, on average, for 9 to 10 months. However, when transplantation is carried out in patients whose disease has progressed while receiving such therapy, results are poor, although the median survival is prolonged to about 14 months in comparison to only 5 to 6 months for all "5-azacitidine failures." On the other hand, patients who are responding or not progressing while receiving hypomethylating treatment have an approximately 30% probability of being transplanted successfully.[30]

The effect of disease risk is modified by the presence of comorbidities; patients with HCT-CI scores of 3 or higher experience

TABLE 1. WHO Classification

Disease	Blood Findings	Bone Marrow Findings
RCUD (RA, RN, RT)	Unicytopenia or bicytopenia*	Unilineage dysplasia $\geq$ 10% of the cells in one myeloid lineage
	No or rare blasts ($<$ 1%)**	$<$ 5% blasts
		$<$ 15% of erythroid precursors are ring sideroblasts
RARS	Anemia	$\geq$ 15% of erythroid precursors are ring sideroblasts
	No blasts	Erythroid dysplasia only
		$<$ 5% blasts
RCMD	Cytopenia(s)	Dysplasia in $\geq$ 10% of the cells in $\geq$ 2 myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes)
	No or rare blasts ($<$ 1%)**	$<$ 5% blasts in marrow
	No Auer rods	No Auer rods
	$<$ 1 $\times$ 10^9/L monocytes	$\pm$ 15% ring sideroblasts
RAEB-1	Cytopenia(s)	Unilineage or multilineage dysplasia
	$<$ 5% blasts**	5%-9% blasts**
	No Auer rods	No Auer rods
	$<$ 1 $\times$ 10^9/L monocytes	
RAEB-2	Cytopenia(s)	Unilineage or multilineage dysplasia
	5%-19% blasts†	10%-19% blasts†
	Auer rods $\pm$†	Auer rods $\pm$†
	$<$ 1 $\times$ 10^9/L monocytes	
MDS-U	Cytopenias	Unequivocal dysplasia in 10% of cells in one or more myeloid lineages when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS
	$<$ 1% blasts**	$<$ 5% blasts
MDS associated with isolated del(5q)	Anemia	Normal to increased megakaryocytes with hypolobated nuclei
	Usually normal or increased platelet count	$<$ 5% blasts
	No or rare blasts ($<$ 1%)	Isolated del(5q) cytogenetic abnormality
		No Auer rods

Abbreviations: WHO, World Health Organization; RCUD, refractory cytopenia with unilineage dysplasia; RA, refractory anemia; RN, refractory neutropenia; RT, refractory thrombocytopenia; RARS, refractory anemia with ring sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RAEB, refractory anemia with excess blasts; MDS-U, Myelodysplastic syndrome-unclassified.
*Bicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U.
**If the marrow myeloblasts percentage is $<$ 5% but there are 2% to 4% myeloblasts in the blood, the diagnostic classification is RAEB-1; cases of RCUD and RCMD with 1% myeloblasts in the blood should be classified as MDS-U.
†Cases with Auer rods and $<$ 5% myeloblasts in the blood and less than 10% in the marrow should be classified as RAEB-2. Although the finding of 5% to 19% blasts in the blood is, in itself, diagnostic of RAEB-2, cases of RAEB-2 may have $<$ 5% blasts in the blood if they have Auer rods or 10% to 19% blasts in the marrow or both. Similarly, cases of RAEB-2 may have $<$ 10% blasts in the marrow but may be diagnosed by the other two findings, Auer rod+, and/or 5% to 19% blasts in the blood.

TABLE 2. IPSS-R Prognostic Scores[5]

	Score						
Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
Marrow blasts (%)	$\leq$ 2		$>$ 2-$<$ 5		5-10	$>$ 10	
Hemoglobin	$\geq$ 10		8-$<$ 10	$<$ 8			
Platelets	$\geq$ 100	50-$<$ 100	$<$ 50				
Neutrophils	$\geq$ 0.8	$<$ 0.8					

Abbreviation: IPSS-R, Revised International Prognostic Scoring System.

survival rates that may be substantially lower than for patients without scored comorbidities.[11,31,32] We have shown, for example, in patients transplanted for chronic myelomonocytic leukemia (considered under the heading of MDS) from HLA-matched related or unrelated donors that the overall survival in remission was 40%. However, a breakdown by HCT-CI showed a probability of 53% for patients with HCT-CI scores of 0 to 2 but only 26% for patients with scores of 3 or higher.[31]

As MDS is primarily a disease of older individuals who often present with comorbid conditions and who are less likely to tolerate high-intensity conditioning regimens, recent studies have analyzed the relevance of disease classi-

fication for the decision of transplantation. Koresh et al[33] used a Markov decision model and quality-of-life utility estimates to assess transplant success in 514 patients with de novo MDS who were age 60 to 79. Results showed that for patients with low- or intermediate-1-risk MDS (by IPSS criteria)[34] and conditioned with reduced-intensity regimens, life expectancy was 38 months on average, compared to 77 months in patients with nontransplanted disease. In patients with intermediate-2 or high-risk MDS, the corresponding figures were 36 and 28 months, clearly showing an advantage for transplantation, associated with a quality-adjusted survival benefit. These data support the recommendation for or against transplantation on the basis of disease stage.

Encouraging results have been achieved recently with treosulfan-based regimens, which are associated with low toxicity and excellent efficacy. In a trial conducted at the Fred Hutchinson Cancer Research Center, 60 patients with MDS or AML were prepared with a regimen of fludarabine (30 mg/m^2 × 5) and treosulfan (12 g or 14 g/m^2 × 3) for HCT from HLA-matched related or unrelated donors. Two-year nonrelapse mortality was less than 10%, and relapse-free survival for patients with standard- or intermediate-risk cytogenetics was 80%.[35] Patients with high-risk karyotype, in contrast, showed long-term relapse-free survival of only 35% to 40%. Ongoing trials suggest that with the addition of low-dose (2 Gy) total body irradiation to fludarabine and treosulfan, relapse-free survival may increase to 65%, even among patients with high-risk cytogenetics.[36]

Although cytogenetics have been shown to have the strongest effect on post-transplant relapse and, as a result, relapse-free survival,[27] emerging data suggest that somatic mutations further modify the outcome. Bejar et al have shown that mutations in p53, DNMT3A, or TET2 each decrease the probability of post-transplant survival by a factor of three to four.[37] On the other hand, data show that mutations in SF3B1 are associated with a superior leukemia-free and overall survival, possibly affecting the decision on and the timing for transplantation.[38]

OUTLOOK

Clearly, more effective strategies are needed for the prevention of GVHD and relapse. Various strategies of post-HCT therapy, for example, with hypomethylating agents or cellular therapy with natural killer cells or genetically modified T cells (directed, for example, at Wilms tumor 1), are currently being explored in efforts to prevent relapse.[39] The use of post-HCT administration of cyclophosphamide, in the hands of several investigators, has been effective in preventing GVHD after HLA-haploidentical transplants and is also being tested in patients receiving HLA-matched transplants where acute or chronic GVHD (or both) occur about in half of all patients and, particularly with unrelated HCT, involvement of the intestinal tract proves life threatening.[23]

The use of HCT in growing numbers of older patients with MDS, even in their 70s, poses special challenges, particularly with the intensity of conditioning. Currently those patients are highly selected, and results cannot be extrapolated to that age segment in general. Further, first-line therapy with steroids, although effective in a portion of patients, is often poorly tolerated in older individuals.[40] Metabolic abnormalities, infections, and long-term effects on muscles and skeleton can severely affect quality of life. Thus, not only comorbidities before HCT but also complications developing after HCT must be prioritized when discussing HCT with older patients, for whom quality of life (rather than quantity of life) is often a top priority.

Clearly, the rapidly expanding understanding of the effect of various mutations in clonal cells will affect disease risk classification and may also lead to novel antirelapse strategies aimed at molecular targets.[41,42]

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LEUKEMIA, MYELODYSPLASIA, AND TRANSPLANTATION

Progress in Myeloproliferative Neoplasms: Biology to Bedside

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Diagnosing and Managing Advanced Chronic Myeloid Leukemia

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OVERVIEW

Clinical staging of chronic myeloid leukemia (CML) distinguishes between chronic phase (CP-CML), accelerated phase (AP-CML), and blastic phase (BP-CML), reflecting its natural history in the absence of effective therapy. Morphologically, transformation from CP-CML to AP/BP-CML is characterized by a progressive or sudden loss of differentiation. Multiple different somatic mutations have been implicated in transformation from CP-CML to AP/BC-CML, but no characteristic mutation or combination of mutations have emerged. Gene expression profiles of AP-CML and BP-CML are similar, consistent with biphasic evolution at the molecular level. Gene expression of tyrosine kinase inhibitor (TKI)–resistant CP-CML and second CP-CML resemble AP/BP-CML, suggesting that morphology alone is a poor predictor of biologic behavior. At the clinical level, progression to AP/BP-CML or resistance to first-line TKI therapy distinguishes a good risk condition with survival close to the general population from a disease likely to reduce survival. Progression while receiving TKI therapy is frequently caused by mutations in the target kinase BCR-ABL1, but progression may occur in the absence of explanatory BCR-ABL1 mutations, suggesting involvement of alternative pathways. Identifying patients in whom milestones of TKI response fail to occur or whose disease progress while receiving therapy requires appropriate molecular monitoring. Selection of salvage TKI depends on prior TKI history, comorbidities, and BCR-ABL1 mutation status. Despite the introduction of novel TKIs, therapy of AP/BP-CML remains challenging and requires accepting modalities with substantial toxicity, such as hematopoietic stem cell transplantation (HSCT).

It is thought that CML is initiated when a hematopoietic stem cell acquires the t(9;22)(q11;34) reciprocal translocation, which the cytogenetic correlate is the Philadelphia chromosome (Ph). Based on the increase in CML incidence in survivors of the atomic bombings on Japan, the latency between this initial event to the clinical manifestation is estimated to be approximately 8 years.[1] Whether or not a clonal genetic lesion predates the acquisition of Ph or whether additional genetic abnormalities are required to produce CP-CML is a matter of debate. However, recent next-generation sequencing studies suggest both scenarios are possible.[2] Without effective therapy, CP-CML invariably progresses to an acute leukemia termed BP-CML, sometimes through an intermediate stage referred to as AP-CML. BP-CML may have a myeloid (70%), B-lymphoid (20%), or mixed phenotype (10%).[3] Observations from the 1920s, when therapeutic options were limited to splenic irradiation and arsenic trioxide, suggest that the natural duration of CP-CML may be approximately 2.5 years. In the developed world, the vast majority of patients are diagnosed in the chronic phase, frequently when an abnormal complete blood count leads to a diagnostic workup. Presentation with AP/BP-CML is more common in countries with lower socioeconomic status, probably reflecting delays in diagnosis as a result of insufficient access to medical care. The term "advanced CML" is not clearly defined and variably used to include AP/BP-CML only or also CP-CML resistant to standard therapy.

DEFINING ADVANCED CHRONIC MYELOID LEUKEMIA: CHRONIC PHASE, ACCELERATED PHASE, AND BLASTIC PHASE

Several different classification systems have been developed to define the phases of CML based on morphologic and clinical criteria, including the International Bone Marrow Transplant Registry (IBMTR), The University of Texas MD Anderson Cancer Center (MDACC), and World Health Organization (WHO) classifications (Table 1). The simultaneous use of different systems has generated considerable confusion, as different classifications may assign patients to different disease phases and some of the criteria lack a precise definition. For example, the WHO definition of AP-CML uses increasing white blood cells and spleen size unresponsive to therapy as defining criteria. Another important discrepancy is the bone marrow or blood blast percentage that defines BP-CML. Whereas the WHO classification uses 20% or greater as the cutoff (in line with acute myeloid leukemia [AML]), MDACC and IBMTR classifications use 30% or greater. The MDACC criteria defining AP-CML were prospectively validated as independent prognostic variables, and

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TABLE 1. Definitions of Accelerated- and Blastic-Phase Chronic Myeloid Lymphoma

	Modified MDACC Criteria*	WHO Criteria	IBMTR
Accelerated Phase	Blood or marrow blasts 15-29%	Blood or marrow blasts 10-19%	Hb < 8 g/dL
	Blood or marrow blasts and promyelocytes ≥ 30%	Blood basophils > 20%	WBC > 100 × 10^9/L
	Blood basophils > 20%	Plts < 100 × 10^9/L or >1,000 × 10^9/L	Plts < 100 × 10^9/L or > 1,000 × 10^9/L
	Plts < 100 × 10^9/L	Increasing spleen size and WBC	Splenomegaly unresponsive to busulfan and hydroxyurea
	CCA/Ph$^+$	CCA/Ph$^+$	Extramedullary disease
			CCA/Ph$^+$
			Blood or marrow blasts > 10%
			Blood or marrow blasts plus promyelocytes > 20%
			Blood basophils and eosinophils > 20%
Blastic Phase	Blood or marrow blasts ≥ 30%	Blood or marrow blasts > 20%	Blood or marrow blasts ≥ 30%
	Extramedullary blasts (apart from spleen)	Extramedullary blast proliferation	Extramedullary blasts (apart from spleen)
		Large foci or clusters of blasts on bone marrow biopsy	

Abbreviations: MDACC, The University of Texas MD Anderson Cancer Center; WHO, World Health Organization; IBMTR, International Bone Marrow Transplant Registry; CCA/Ph$^+$, clonal cytogenetic abnormalities in Ph$^+$ cells; Plts, platelets; WBC, white blood cells; Hb, hemoglobin.
*Commonly used in clinical trials.

were used (in some cases with minor adaptations) in the major practice-defining prospective clinical trials and therefore are recommended.[4-6] In the future, molecular classifications may replace morphology and blood counts. An uncommon clinical presentation is chloroma, which establishes a diagnosis of BP-CML, irrespective of marrow and blood. Biopsy is required and a diagnosis of chloroma requires the presence of blasts, whereas mature granulocytic infiltrates in extramedullary sites other than the spleen or liver may be reactive to inflammation or infection and should not be confused with BP-CML.

The Sokal and Hasford scores were developed in patients treated with chemotherapy or interferon alfa (IFN-α), respectively, but were subsequently validated in prospective TKI studies. The EUTOS score was developed in a cohort of patients treated with imatinib, but was not universally confirmed in subsequent studies.[10] All three prognostication systems are based on laboratory and clinical parameters obtained in untreated patients. Any form of therapy, including hydroxyurea, may generate misleading results and must be avoided. Although patients with high Sokal or Hasford scores are less likely to achieve deep responses to TKIs and

RISK STRATIFICATION IN CHRONIC-PHASE CHRONIC MYELOID LEUKEMIA

Clinical scoring systems to risk stratify CP-CML include the Sokal, Hasford (European), and EUTOS scores (Table 2).[7-9]

KEY POINTS

- Chronic myeloid leukemia (CML) progresses in phases that represent the most fundamental risk stratification.
- Multiple different somatic mutations have been associated with transformation from chronic to advanced CML.
- Disease progression while receiving first-line tyrosine kinase inhibitor (TKI) therapy and accelerated or blastic phase CML are associated with reduced overall survival.
- BCR-ABL1 kinase domain mutations are the best characterized mechanism of TKI resistance, but fail to explain many cases of clinical resistance.
- Selection of salvage therapy depends on prior TKI exposure, comorbidities, and BCR-ABL1 mutation status.

TABLE 2. Risk Stratification in Chronic-Phase Chronic Myeloid Lymphoma

Risk Score	Calculation	Risk Groups
Sokal	Exp 0.0116 × (age − 43.4) + 0.0345 × (spleen − 7.51) + 0.188 × [(platelet count ÷ 700)^2 − 0.563] + 0.0887 × (blast cells − 2.10)	Low: < 0.8
		Intermediate: 0.8-1.2
		High: > 1.2
Hasford	0.666 when age ≥ 50 + (0.042 × spleen) + 1.0956 when platelet count > 1,500 × 109L + (0.0584 × blast cells) + 0.20399 when basophils >3% + (0.0413 × eosinophils) × 100	Low: ≤ 780
		Intermediate: 781-1,480
		High: > 1480
EUTOS	Spleen × 4 + basophils × 7	Low risk: ≤ 87
		High risk: > 87

Abbreviation: EUTOS, European Treatment Outcome Study.

have a higher risk or progression, they are not considered as having advanced CML. Given that the distinction between CP-CML and BP-CML can hinge on minute differences in the white blood differential count, it is obvious that the separation of high-risk CP-CML from AP-CML may be more theoretical than practically relevant. Consistent with this, gene expression profiling studies on CP-CML, using mononuclear cells or CD34$^+$ cells, have revealed overlap between poor-prognosis CP-CML and BP-CML.[11-13]

MOLECULAR UNDERPINNING OF BLASTIC TRANSFORMATION

The salient morphologic feature of BP-CML is loss of cellular differentiation capacity, which may occur suddenly or gradually through the intermediate stage of AP-CML. Progression is frequently associated with clonal cytogenetic evolution. The distinction between major (+8, isochromosome 17q, additional Ph, +19) and minor route abnormalities (all others) is of limited clinical significance once transformation has occurred. However, in newly diagnosed CP-CML major route abnormalities are associated with a poor outcome with imatinib treatment.[14] At the molecular level, multiple somatic mutations have been identified upon transformation, but there is no characteristic molecular abnormality (Table 3).[15] Unsurprisingly, lymphoid BP-CML resembles Ph$^+$ acute lymphoblastic leukemia (ALL), whereas mutations typical for AML and myelodysplastic syndromes are dominant in myeloid BP-CML. Core binding factor mutations such as AML1-ETO and CBFB-MYH11 are uncommon in BP-CML, suggesting that the differentiation block of BP-CML has a different molecular basis. Epigenetic dysregula-

TABLE 3. Mutations Associated with Blastic-Phase Chronic Myeloid Lymphoma

Mutation/Mutated Gene	% Prevalence
Double Ph	38%
Isochromosome 17q	30% (myeloid)
Trisomy 8	53% (lymphoid)
Trisomy 19	23% (myeloid)
p53	20-30% (myeloid)
p16	50% (lymphoid)
NUP98-HOXA9	NR
AML1-EVI1	NR
GATA-2	18% (lymphoid)
RUNX1	38% (myeloid)
CDKN2A/B	50% (lymphoid)
IKZF1	55% (lymphoid)
ASXL1	20.5% (myeloid)
TET2	7.7% (myeloid)
WT1	15.4% (myeloid)
NRAS/KRAS	5.1/5.1% (myeloid)

Abbreviation: NR, not reported.

tion is likely to play a major role, for example through increased BCR-ABL1 expression that in turn suppresses the myeloid transcription factor CEBPA.[16,17]

APPROACH TO THE PATIENT PRESENTING WITH ACCELERATED-PHASE/BLASTIC-PHASE CHRONIC MYELOID LEUKEMIA

As presentation of CML in AP or BP is uncommon in the developed world, there is limited data for this group of patients. However, second-generation TKIs are preferred over imatinib. In the salvage setting, dasatinib has shown slightly higher response rates and more durable responses in CML-AP and is currently the only second-generation TKI approved for BP-CML.[18] In the case of blastic transformation, TKIs are usually combined with AML- or ALL-type multiagent chemotherapy, whereas this is not typically the case for AP.[19] All patients with AP/BP-CML should be considered for an allogeneic stem cell transplant, with TKI therapy used to restore a second chronic phase and bridge the time to transplant. Therefore, human leukocyte antigen typing and a transplant consultation are essential parts of the initial workup for patients who present in AP/BP. Whether or not to proceed to allografting in a patient with AP/BP-CML who attained a very good response to TKI can pose an extremely challenging clinical decision, and it is wise to discuss this eventuality before starting TKI therapy. Transplant risk, comorbidities, and the patient's personal preferences are critical factors.

DEFINING TREATMENT FAILURE
Resistance to Tyrosine Kinase Inhibitors

Clinical TKI resistance is grouped into primary and acquired resistance. At a mechanistic level, resistance can be classified as BCR-ABL1–dependent or BCR-ABL1–independent. In BCR-ABL1–dependent resistance, there is reactivation of BCR-ABL1 kinase, which implies that responses may be recaptured if BCR-ABL1 inhibition is restored. In BCR-ABL1–independent resistance, alternative pathways substitute for BCR-ABL1 kinase activity.[20]

BCR-ABL1 Kinase Domain Mutations

The best characterized mechanism of TKI resistance is point mutations in the *BCR-ABL1* kinase domain that impair drug binding.[21] Solving the crystal structure of ABL1 in complex with an imatinib analog was instrumental to understanding how kinase domain mutations cause resistance.[22] In contrast to expectations, imatinib was found to bind an inactive conformation of ABL1, with the activation loop of the kinase in a closed position. Additionally, there was extensive downward displacement of the ATP-binding loop. Mutations in the kinase domain can cause resistance by steric hindrance or elimination of hydrogen bonds, most impressively in the T315I mutation at the gatekeeper position. A different type of mutation affects

the ATP-binding loop, preventing the rearrangements required for optimal drug binding. Examples include Q252H, Y253(H/F), and E255(K/V). Last, mutations in the activation loop such as H396P stabilize an open conformation, to which imatinib cannot bind.[23] Although imatinib is vulnerable to a broad range of mutations, the spectrum is much more limited for nilotinib and dasatinib, reflecting their greater potency and, in the case of dasatinib, less stringent binding requirements.[24] Clinical resistance mutations are precisely predicted by in vitro assays, which enable the development of preemptive strategies to overcome this type of resistance.[25-27] Mutation testing is recommended upon disease progression and if milestones are not met. Most laboratories use Sanger sequencing, which has a sensitivity of approximately 20% mutant allele. This level of sensitivity seems to provide the right balance between sensitivity and specificity. More sensitive assays such as next-generation sequencing are under development and may replace Sanger sequencing in the future. Biochemical and cell proliferation data have been used to rank kinase domain mutations according to the degree of TKI resistance they confer.[28] Although these data are based on in vitro studies, they tend to correlate with clinical responses.[29,30] However, correlations are not as tight as one might suspect, suggesting that additional mechanisms govern clinical resistance. The exception to this rule is the T315I mutation that confers complete resistance to all approved TKIs, except ponatinib. For several other mutants, the difference in sensitivity is sufficient to support the use of dasatinib over nilotinib, or vice versa (Fig. 1). An in-depth discussion of the many reported mutations and their sensitivity profiles is beyond the scope of this chapter and the reader is referred to detailed reviews of this subject.[31-33]

Activation of Alternative Signaling Pathways

In contrast to kinase domain mutations, BCR-ABL1 kinase–independent resistance is less well understood and seems to involve multiple different mechanisms. For example, activation of SRC family kinases, MAP kinase, STAT5, SYK, and PI3K have all been associated with TKI resistance, despite sustained inhibition of BCR-ABL1.[34-38] Extrinsic factors such as cytokines may also play a role.[39,40] Targeting these diverse pathways is therapeutically challenging and common downstream effector molecules such as pSTAT3 or processes such as nuclear cytoplasmic transport may be more promising.[41-43]

FIGURE 1. Activity of Imatinib, Bosutinib, Dasatinib, Nilotinib, and Ponatinib against Mutated Forms of BCR-ABL1

		Imatinib	Bosutinib	Dasatinib	Nilotinib	Ponatinib
	Parental	10.8	38.3	568.3	38.4	570.0
	WT	1	1	1	1	1
P-loop	M244V	0.9	0.9	2.0	1.2	3.2
	L248R	14.6	22.9	12.5	30.2	6.2
	L248V	3.5	3.5	5.1	2.8	3.4
	G250E	6.9	4.3	4.4	4.6	6.0
	Q252H	1.4	0.8	3.1	2.6	6.1
	Y253F	3.6	1.0	1.6	3.2	3.7
	Y253H	8.7	0.6	2.6	36.8	2.6
	E255K	6.0	9.5	5.6	6.7	8.4
	E255V	17.0	5.5	3.4	10.3	12.9
C-helix	D276G	2.2	0.6	1.4	2.0	2.1
	E279K	3.6	1.0	1.6	2.0	3.0
	E292L	0.7	1.1	1.3	1.8	2.0
ATP binding region	V299L	1.5	26.1	8.7	1.3	0.6
	T315A	1.7	6.0	58.9	2.7	0.4
	T315I	17.5	45.4	75.0	39.4	3.0
	T315V	12.2	29.3	738.8	57.0	2.1
	F317L	2.6	2.4	4.5	2.2	0.7
	F317R	2.3	33.5	114.8	2.3	4.9
	F317V	0.4	11.5	21.3	0.5	2.3
SH2-contact	M343T	1.2	1.1	0.9	0.8	0.9
	M351T	1.8	0.7	0.9	0.4	1.2
Substrate binding region	F359I	6.0	2.9	3.0	16.3	2.9
	F359V	2.9	0.9	1.5	5.2	4.4
A-loop	L384M	1.3	0.5	2.2	2.3	2.2
	H396P	2.4	0.4	1.1	2.4	1.4
	H396R	3.9	0.8	1.6	3.1	5.9
C-terminal lobe	F486S	8.1	2.3	3.0	1.9	2.1

IC$_{50}$-fold increase (WT = 1)

Sensitivity similar to native BCR-ABL1	≤ 5
Moderately resistant	5.1 - 10
Highly resistant	>10

Cell proliferation IC$_{50}$ values of the indicated TKIs are shown against BCR-ABL1 single mutants. The color gradient demonstrates IC$_{50}$ sensitivity for each TKI relative to its activity against cells expressing native BCR-ABL1. Note that clinical activity is also dependent on additional factors, such as drug concentrations achieved in the plasma of patients.

Adapted with permission from Redaelli et al.[64]

APPROACH TO THE PATIENT WITH TYROSINE KINASE INHIBITOR RESISTANCE

The European Leukemia Net and the National Comprehensive Cancer Network have defined therapeutic milestones for patients receiving TKI therapy (Table 4).[6,44] Although both systems are generally aligned, the European Leukemia Net uses the category of "warning" to denote a situation that does not meet the criteria for failure, but gives rise to concern that a poor outcome is possible. Failure to achieve therapeutic milestones is consistent with primary resistance. Loss of response from a given level suggests acquired TKI resistance. Both should trigger a thorough evaluation. TKI resistance is a clinically important diagnosis that is associated with inferior outcomes compared with those of the average CML population. The first call of order is to assess medication adherence through a thorough history. Drug level testing may be useful in isolated cases, but is not widely available. Additionally, patients have been found to make up for skipped doses during the last few days before the office visit.[45] Second, drug interactions must be considered, especially in patients on multiple comedications, including over-the-counter remedies such as St. John's Wort, which can drastically lower imatinib plasma concentrations.[46] Predicting drug interactions in patients on polypharmacotherapy is challenging, particularly in cases with impaired renal or hepatic function and consultation of a clinical pharmacologist is advisable. A frequent challenge is a rise in the level of *BCR-ABL1* mRNA as assessed by quantitative polymerase chain reaction. Interpretation of changes in *BCR-ABL1* mRNA must take into account the performance of the diagnostic laboratory. In most cases, only rises greater than five-fold or greater than 10-fold are clinically relevant, particularly in patients with a low level of residual disease.[47] In the absence of other signs of relapse, repeating the *BCR-ABL1* quantitative polymerase chain reaction in 4 to 6 weeks is recommended, before additional diagnostic studies are initiated. If nonadherence or drug interactions are unlikely, a complete resistance work-up is indicated that includes a physical exam, complete blood count, bone marrow aspirate and biopsy, bone marrow metaphase karyotyping, and *BCR-ABL1* mutation analysis. TKI resistance defines a high-risk situation and should be approached as a diagnosis with important clinical implications. Key pieces of information derived from this workup are disease phase, *BCR-ABL1* mutation status, and karyotype, including CCA/Ph$^+$.

Progression of Chronic-Phase Chronic Myeloid Leukemia

Progression with first-line imatinib. Patients whose disease develops resistance to first-line imatinib, but who are still in chronic phase, are switched to a second-generation TKI, the selection of which is based on the first-line TKI, past medical history to avoid specific side effects, and (if present) the type of *BCR-ABL1* mutation (Fig. 1). Patients with first-line imatinib failure have a 40% to 50% chance of achieving complete cytogenic response (CCyR) on a second-generation TKI.[48,49] Overall, however, the prognosis of these patients is guarded. In a retrospective study, overall and progression-free survival at 4 years were 81.9% and 35.3%, respectively, indicating that most patients will eventually require an alternative therapy.[50] Close molecular monitoring is required. One study showed that only 7% of patients without a minor cytogenetic response ($\leq 65\%$ Ph$^+$ metaphases) at 3 months were in major cytogenic response at 12 months, whereas major cytogenic response at 12 months predicted progression-free and overall survival (OS).[51] Another study reported that achieving less than 10% BCR-ABL1^{IS} at 3 months was predictive of OS (91.3% vs. 72.1%, p = 0.02) and event-free survival (49.3% vs. 13.0%, p < 0.001). Taken together, these data suggest that the 3-months evaluation is critical for determining whether the first salvage is likely to work.

Progression during second-generation tyrosine kinase inhibitor therapy and failure of multiple tyrosine kinase inhibitors. Selecting the optimal approach in patients in whom second-generation TKI first-line therapy fails is challenging. Current guidelines recommend using an alternative second-generation TKI, but limited data are available regarding the efficacy of this strategy. Retrospective studies of dasatinib, nilotinib, and bosutinib as third-line therapies after failure of imatinib show limited efficacy, with CCyR rates of approximately 20%.[52,53] Moreover, responses are frequently not durable, raising the question of ponatinib as a more effective and durable salvage therapy. In the Ponatinib Ph$^+$ ALL and CML Evaluation (PACE) trial, 46% of CP-CML patients achieved CCyR, 91% of which were maintained at 12 months. In most (93%) patients, two or more TKIs had previously failed, making ponatinib a strong consideration for patients in whom multiple TKIs have failed.[54] Ponatinib is the drug of choice for patients with the BCR-ABL1^{T315I} mutation. The

TABLE 4. Therapeutic Milestones: National Cancer Center Network versus European Leukemia Net

Month		Optimal	Warning	Failure
3	ELN	Ph+ $\leq$ 35% or BCR-ABL1 < 10%	Ph+ 65-95% or BCR-ABL1 > 10%	No CHR or Ph+ > 95%
	NCCN	Ph+ $\leq$ 35% or BCR-ABL1 $\leq$ 10%	NA	Ph+ > 35% or BCR-ABL1 > 10%
6	ELN	Ph+ 0% and/or BCR-ABL1 < 1%	Ph+ 1-35% and/or BCR-ABL1 1-10%	Ph+ > 35% and/or BCR-ABL1 > 10%
	NCCN	Ph+ $\leq$ 35% or BCR-ABL1 $\leq$ 10%	NA	Ph+ > 35% or BCR-ABL1 > 10%
12	ELN	BCR-ABL1 < 0.1%	BCR-ABL1 0.1-1%	Ph+ > 0% BCR-ABL1 > 1%
	NCCN	Ph+ 0%	NA	Ph+ > 0%

Abbreviations: ELN, European Leukemia Net; Ph+, Ph+ bone marrow metaphases; NCCN, National Cancer Center Network; NA, not applicable; CHR, complete hematologic remission.

broad range efficacy of ponatinib must be balanced against its substantial cardiovascular toxicity, which is enhanced by preexisting risk factors such as diabetes, hypercholesterolemia, and hypertension.[54] Failure of ponatinib indicates a patient is a candidate for non-TKI therapies, including omacetaxine, a clinical trial, or HSCT.[44] This is particularly true for patients with compound mutations that include T315I as one component and may confer resistance to all currently approved TKIs.[28] Dense qPCR monitoring is critical for patients in whom second-generation TKIs failed, and those in whom multiple TKIs have failed. When to proceed to HSCT in a patient with CP-CML is a difficult clinical decision that must take into account the transplant risk as well as the risk of progression to AP/BC-CML. It is good clinical practice to refer any transplant-eligible patient with progression on first-line therapy to a transplant center for an initial evaluation and preliminary clarification of donor options.

Progression to Accelerated-Phase/Blastic-Phase Chronic Myeloid Leukemia

Patients who progress to AP/BP-CML are treated with the appropriate TKI, taking into account prior TKI exposure history and *BCR-ABL1* mutation status. Given the limited therapeutic options, more TKI toxicity is acceptable. Decisions whether or not to combine TKI salvage with chemotherapy must be individualized based on performance status and the availability of allogeneic stem cell transplant as a potentially curative salvage strategy.[19] Given the absence of controlled studies in this fortunately rare patient population, the value of adding chemotherapy is not completely clear, particularly in patients with myeloid transformation. All eligible patients should be offered an allogeneic stem cell transplant, and avoiding unnecessary toxicity in potential transplant patients is an important consideration.

ALLOGENEIC STEM CELL TRANSPLANTATION

Allogeneic HSCT was the first treatment modality that restored Ph-negative hematopoiesis and induced durable responses.[55] Before the introduction of imatinib, allografting was recommended to all eligible patients and even today it is still regarded as the only therapy with curative potential. Only one study prospectively compared allotransplant versus drug therapy. Newly diagnosed patients with CML-CP were biologically randomly assigned to a matched sibling transplant versus IFN-based drug therapy, the best nontransplant treatment available when the trial was initiated.[56] Patients managed with drug therapy had superior survival, with the biggest difference observed in low-risk patients. After approximately 8 years, the survival curves crossed, suggesting that transplant would be superior in the long-term if IFN was the alternative. However, given the efficacy of TKIs in the first-line setting, and that early transplant-related mortality is clearly higher than the risk of early disease progression, allotransplant is no longer justifiable in newly diagnosed patients with CML-CP, except in unusual circumstances.[57]

Risk scores for allografting in CML were developed by the European Group for Blood and Marrow Transplantation (EBMT) in the pre-imatinib era and identified disease duration of longer than 12 months, more advanced disease, higher age, unrelated donor type, and the combination of a male recipient with a female donor as adverse prognostic factors.[58] Disease phase had the greatest effect on outcome. Although somewhat historic, the EBMT score is still useful for prognostication. There is consensus that allotransplant should be offered to all patients with progression to AP/BP. A more individualized approach is required for patients in whom dasatinib or nilotinib have failed in chronic phase, given that ponatinib is effective, albeit at the cost of cardiovascular toxicity.[54] Fortunately, there is no evidence that imatinib or other TKIs before allografting negatively affect the outcome. On the contrary, for unknown reasons, imatinib before allotransplant seems to reduce the risk of chronic graft-versus-host disease and possibly relapse risk.[59-61] Results from the German CML study group reassert the importance of transplanting patients while they are still in chronic phase: 3-year OS was 91% for patients transplanted in CP after imatinib failed versus 59% for patients transplanted in AP/BP.[62] There is an emerging consensus that bone marrow is preferred over peripheral blood stem cells in patients with CML-CP, in whom graft-versus-host disease is a greater concern than disease control.[63] This assessment is different for patients with transformation to AP/BP, even if they have achieved a second chronic phase. High relapse–risk patients should receive a TKI post-transplant; *BCR-ABL1* mutation analysis at the time of resistance will help match the optimal TKI to individual patients. Given the high median age at the time of diagnosis, many patients will be eligible only for reduced intensity conditioning regimens. An in-depth discussion of the various conditioning regimens, selection of bone marrow versus peripheral blood stem cells, and post-transplant immunosuppression is presented elsewhere.

PERSPECTIVE

Despite the unparalleled success of TKI in CML, progression during first-line TKI therapy, and transformation to accelerated- or blastic-phase continue to carry a poor prognosis. Although BCR-ABL1 mutations are a well-established mechanism of TKI resistance, many cases of clinical resistance remained mechanistically unexplained and are thought to be a result of activation of alternative signaling pathways. In these patients, salvage therapies are currently nonspecific. The hope is that diverse upstream pathways may activate a limited set of downstream effector molecules, thus providing an opportunity for rationally targeted therapies that are applicable to a wider population of patients. Early identification of patients with TKI failure or at risk of transformation is critical, so that therapy can be adjusted in a timely fashion to maximize the chances of successful salvage therapy. Despite the introduction of new TKIs such as ponatinib, the prediction is that allogeneic stem cell transplant will retain its position as the salvage therapy of choice for patients who progress to AP/BC-CML.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked "L" indicate leadership positions. Relationships marked "I" are those held by an immediate family member; those marked "B" are held by the author and an immediate family member. Institutional relationships are marked "Inst." Relationships marked "U" are uncompensated.

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From Philadelphia-Negative to *JAK2*-Positive: Effect of Genetic Discovery on Risk Stratification and Management

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OVERVIEW

The 2005 discovery of the *JAK2* mutation redefined the diagnosis and natural history of myeloproliferative neoplasms (MPNs). Most importantly, this improvement in the pathobiologic conceptualization has focused our evolution of this field from being defined as what it is not (e.g., Philadelphia [Ph]-negative) to what it is (e.g., *JAK2*-positive, *CALR*-positive) in the majority of MPN cases. In the ensuing 10 years, the field has experienced a paradigm shift in terms of understanding of the biologic basis of the development of MPNs, an explosion of knowledge of the genetics of MPNs, and has translated disease knowledge into effective targeted therapies. With greater uniformity and agreement on the diagnosis and differences among the individual MPNs, augmented by improved cytogenetic and molecular classification, attention has turned now to addressing the need for uniformity in risk stratification of patients in the clinic for both disease complications and disease transformation. This article will highlight the developments in the field with regard to risk stratification and prognostication in MPNs with focus on the clinical aspects of the patient who presents with either essential thrombocytosis (ET), polycythemia vera (PV), or myelofibrosis (MF).

Myeloproliferative neoplasms represent a family of clonal hematopoietic stem cell disorders that exhibit a wide variety of clinical, biologic, and phenotypic heterogeneity. MPNs serve as the model of acquired somatic genetic lesions as the causal basis of cancer (so-called drivers), from the first genetic lesion ascribed to cancer, the Philadelphia (Ph) chromosome in chronic myelogenous leukemia (CML), to the more recent discoveries of lesions in *JAK2, MPL,* and *CALR* in what were previously called Ph-chromosome–negative MPN. MPNs cause a substantial amount of morbidity and mortality during a patient's lifetime, including increased cardiovascular, thrombotic, and hemorrhagic events, and increased lifetime risk for transformation to acute myeloid leukemia (AML), bone marrow failure, or MF. In the 10 years since the *JAK2V617F* discovery, the MPN field has experienced a profound increase in both clinical and basic research with regard to further understanding of the pathobiologic basis for the disease, especially illustrated by the more recent discoveries of diagnostic and prognostic significance of *JAK2, MPL, CALR, ASXL1*, and other molecular markers. Importantly, genetic discovery in CML and MPN have been translated to effective, targeted therapy, capable of altering the natural history of the MPN.[1-6] This review will focus on the most recent advances in risk stratification of the patient with MPN, and how risk stratification can be translated to disease- and patient-specific therapy.

ACQUIRED SOMATIC MUTATION IN THE MPN: IDENTIFICATION OF CAUSAL LESIONS

Chronic myeloproliferative disorders (MPDs) were recognized as clinical entities in the 19th century, but the 20th century brought precise clinical classification and their genetic basis into being. The 21st century has, and continues to, unravel their causal genetic basis. The primary nature of bone marrow's overproduction was compared with that of leukemia, and both CML and PV were considered as neoplasms of the hematopoietic tissue. William Dameshek theorized that these entities might be driven by a shared stimulus intrinsic to the marrow itself, and coined the term MPDs.[7] The identification of the Ph chromosome as specific to CML and not to the rest of the MPD class was not only an advance in disease classification within MPNs, but, ultimately, confirmed the causal association of an acquired genetic lesion in the generation of human cancer.[8]

Given the similarities of Ph-chromosome–negative MPN to Ph-positive–MPN (stem cell basis, overproduction of mature myeloid elements, tendency to evolve to MF or acute leukemia), lesions in tyrosine kinase pathways critical to erythropoietin, thrombopoietin, and granulocyte-colony stimulating factor signal transduction were investigated. Advances in DNA sequencing technology led several investigators to resequence the *JAK2* gene in patients with PV because of its specific activity in primary PV cells, its identity as a ty-

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TABLE 1. Acquired Somatic Lesions in the World Health Organization 2008 Myeloproliferative Neoplasm Classification

	Lesions	Combined Frequency
Polycythemia Vera	JAK2V617F, JAK2 exon 12	99%
Essential Thrombocythemia	JAK2V617F, CALR, MPL	Approximately 80%
Primary Myelofibrosis	JAK2V617F, CALR, MPL	Approximately 80%
Chronic Myelogenous Leukemia	BCR-ABL1	100%
Chronic Neutrophilic Leukemia	CSFR3	Approximately 80%
Mastocytosis	KIT	Approximately 80%

rosine kinase, or its location in the chromosome 9p loss of heterozygosity region highly prevalent in MPNs.[9-12] *JAK2* mutations are identified in nearly 100% of patients with PV, and are also highly prevalent in patients with thrombocytosis (ET) and primary MF (PMF; Table 1). Like BCR-ABL1, evidence that driver lesions are causative in MPNs are as follows: recapitulation of MPN disease in transgenic murine models,[13-15] gene-dosage effect of *JAK2V617F* on MPN phenotype,[16] and hematologic remissions corresponding to molecular remissions.[4,5] The *BCR-ABL* and *JAK2* discoveries also have hastened the discovery of other causative MPN lesions by allowing for enrichment of lesion-negative MPNs in global resequencing studies.[14,17-19] Table 1 outlines the high-frequency causal driver lesions identified to date and their relative frequency in MPNs. Given the relative prevalence of the various MPNs and the frequency of driver lesions within MPNs, *JAK2V617F* is the most common lesion in this group. The term Ph-chromosome–negative MPN was applied because the Ph discovery was the first. This term is no longer relevant as identified lesions in Table 1 now have come to define their clinical entities.

OVERVIEW OF RISK ASSESSMENT IN MPNs

In contrast to CML, a disease with a fairly uniform sequential natural history driven by BCR-ABL1, marked variability ex-

KEY POINTS

- Genetic discovery has transformed the diagnosis of the chronic myeloproliferative neoplasms (MPNs).
- Risk stratification in MPNs has been redefined by genetic discovery.
- Global risk assessment for MPNs includes disease-specific and patient-specific risk factors.
- Genetic discovery has informed both thrombosis and disease transformation risk stratification.
- Inclusion of constitutional symptoms into prognostic scoring systems signifies the continued importance of patient-reported outcomes in risk stratification.

ists in the natural history of *JAK2-, CALR-, MPL-,* and *KIT*-mutation–positive disease. For instance, *JAK2V617F* in many individuals is latent and may be asymptomatic or aphenotypic for undisclosed periods, as evidenced by its detection in large unselected population surveys.[20] Moreover, cells that have acquired *JAK2V617F* often acquire an additional copy of *JAK2V617F* via mitotic recombination events, such that *JAK2V617F* mutation dosage is a variable to be accounted for both at diagnosis and during disease monitoring. In these diseases, particularly in *JAK2V617F*-positive MPN, factors such as age at diagnosis, sex, treatment exposure, host genetic background, gene dosage, and other acquired genetic lesions, to a large part, contribute to risk for disease acquisition,[21,22] disease evolution or progression, and thrombosis.[23,24] Thus, risk stratification in MPNs must take into account disease class, specific genetic lesions, lesion burden, and host factors and requires large observational prospective cohorts to establish risk. Estimating risk throughout decades of disease is challenging and often confounded by the individual, and by the lack of knowledge of somatic mutations and their roles. In diseases where survival is measured in decades, risk assessment includes not only long-term risks of disease evolution or transformation, but also ongoing symptom burden risk assessment.

RISK STRATIFICATION IN MPNs
Essential Thrombocytosis

ET is an MPN that features a risk for morbidity and mortality secondary to either thrombotic or hemorrhagic events, as well as transformation to PV, MF, and AML, and represents a distinct entity from PV.[25] Historically, underlying molecular abnormalities of ET remained elusive until discovery of the *JAK2V617* mutation (present in 50% to 60% of cases), *MPL* mutations (4% of cases), and, most recently, *CALR* mutations (15% to 24% of cases; Table 1).[26,27] In terms of thrombosis risk stratification in the clinic, a dual risk factor system has been used based on older age of the patient and a personal history of prior thrombotic (or hemorrhagic) events.[28] Several groups have subsequently put forward additional clinical and laboratory features to be considered. In 2012, the International Working Group for Myeloproliferative Neoplasms Research and Treatment reported on the International Prognostic Score for Essential Thrombocytosis (IPSET).[29] This study analyzed 867 patients with World Health Organization (WHO)-defined ET and found that three factors informed prognosis by multivariate analysis: (1) age 60 or older, (2) white blood cells (WBC) of 11K/uL or greater, and (3) personal history of a thrombotic event. Ultimately, patients were put into one of three risk groups: low, intermediate, and high risk. The IPSET model was able to predict significant differences in survival (median overall survival: low risk, not reached; intermediate risk, 24.5 years; and high risk, 13.8 years). Additionally, the model had the ability to predict thrombotic event rate occurrence. It was unable to account for transformation to MF.

Another recent ET scoring system from a retrospective study focused on the risk for thrombosis in patients with ET, termed the IPSET-thrombosis model.[30] This important

model was validated with internal and external datasets, again demonstrating improved prognostication for risk for thrombosis among patients with ET. Among 891 patients with WHO-classified ET, multivariate analysis and risk scoring found four factors to be significant in terms of predicting thrombotic risk: (1) age older than 60, (2) prior thrombotic history, (3) cardiovascular risk factors, and (4) *JAK2V617* mutation positivity. The model demonstrated three distinct at-risk thrombotic groups: low risk, 1.03% of patients per year; intermediate risk, 2.35% of patients per year; and high risk, 3.56% of patients per year. Notably in this model, the presence of WBC count is removed as a significant factor, and, instead, both cardiovascular risk factors and the *JAK2V617* mutation are added and demonstrate significance. As this model is based on retrospective data, the prospective validation of this model will be warranted and the presence of leukocytosis and presence of *JAK2V167* mutation and its corresponding allele burden and overall thrombotic risk will need to be further explored, as prior reports have demonstrated that a higher JAK2 allele burden may not necessarily correlate with a higher thrombotic risk in all patients with ET.[31]

In a recent study of 1,150 patients with ET from four Italian centers, Finazzi et al retrospectively sought to analyze if the presence of the newly defined *CALR* mutation would affect prediction of thrombosis by the IPSET-thrombosis model.[32] Among the 1,150 patients, 164 patients (14%) were found to be *CALR* mutated. There was a higher incidence of *CALR* mutation among the low- and intermediate-risk groups as compared with the high-risk IPSET group, and there was a trend toward lower rate of thrombosis noted in the patients with *CALR*-mutated disease as compared with patients with *JAK2V617*-mutated disease (1.30% vs. 1.95% of patients per year), but this was not significant. This finding, as noted by the authors, was mitigated by the fact that *CALR* mutation was also more commonly found among patients with ET with fewer prior thrombotic events and younger patients (Table 2).

ET, regardless of genetic driver, carries significant risks during the lifetime of a patient for transformation to PV and MF. Transformation to PV is a function of time and is closely associated with *JAK2V617F*-positive status, in addition to increasing JAK2V617F allele percentage. Post-ET MF, in con-

TABLE 2. Thrombotic Risk Factors Associated with the Myeloproliferative Neoplasm

Risk Factor	Comments
MPN class	PV > MF > ET
Prior thrombotic event	
Presence of cardiovascular risks	
Age > 60	
Hematocrit > 45%	Validated in PV
JAK2V617F	Strongly associated with BCS

Abbreviations: MPN, myeloproliferative neoplasm; PV, polycythemia vera; ET, essential thrombocytosis; BCS, Budd-Chiari syndrome.

TABLE 3. Risk Factors for Disease Evolution in Myeloproliferative Neoplasm

Evolution	Clinical Risk Factors	Genetic Risk Factors
ET to PV	Disease duration	JAK2V617F, JAK2V617F allele %
ET to MF	Disease duration, male sex, age	JAKV617F allele %, ASXL1, 20q deletion, 13q deletion, trisomy 8
PV to PPVMF	Disease duration	Trisomy 9, ASXL1, 20q deletion, 13q deletion, trisomy 8
MPN to AML	Age, disease duration, karyotypic complexity, myelofibrosis phase, P32, alkylator exposure	JAK2V617F allele %, complex karyotypic lesions, TP53, RUNX1 lesions

Abbreviations: ET, essential thrombocytosis; PV, polycythemia vera; MF, myelofibrosis; PPVMF, postpolycythemia vera myelofibrosis; MPN, myeloproliferative neoplasm; AML, acute myeloid leukemia.

trast, occurs in all ET settings, and is associated with not only disease duration, but also acquisition of additional genetic lesions and male sex (Table 3).[33]

Polycythemia Vera

Historically, risk stratification in PV incorporated age of the patient (older than 65) and prior thrombotic history.[34] More recently, Tefferi et al reviewed outcomes among a large group of patients (1,545 patients) with WHO-specified PV.[24] In this multivariate analysis, the authors found that leukocytosis, advanced age, abnormal cytogenetics, and history of a venous thrombotic event portend a more adverse outcome in terms of overall survival. This model system also further analyzed factors important for predicting transformation to AML, and found that three out of the four factors for survival were still significant for this outcome (all but venous thrombotic event; Tables 2 and 3).

About 20% of patients with PV may experience a thrombotic event during the course of their disease. Thrombotic events occur on the arterial and venous circulation, microvascular, or thromboembolic, such as transient ischemic attacks, myocardial infarction, deep venous thrombosis, or pulmonary embolism. Venous thrombosis in unusual circulations may occur in the patient with PV, particularly in the portal and hepatic (splanchnic), splenic vein, and cerebral venous sinuses. An important element in risk stratification of the patient with PV is a comprehensive assessment of a patient's underlying risk factors for thromboembolism, including an understanding of the patient's cardiovascular risk factors, including smoking use and history.[35] The importance of hematocrit control, in addition to controlling traditional cardiovascular risks, was established by the CYTO-PV Collaborative Group, whereby an aggressively pursued threshold of hematocrit 45 or greater resulted in a three- to four-times risk reduction in terms of cardiovascular morbidity and mortality, as compared with the group with less strict hematocrit regulation.[36]

Thrombotic risk in MPNs has also led to risk stratification in patients with occurrence of idiopathic Budd-Chiari syn-

drome (BCS) and portal vein thrombosis (PVT). In a series by Kiladjian et al, 241 patients with splanchnic vein thrombosis (SVT) were examined. *JAK2V617F* mutation was found in 45% of the BCS cases, and 34% of the PVT cases; whereas, *JAK2* exon 12 and *MPL* mutations were not identified in any.[37] A meta-analysis showed that because of the close association of *JAK2V617F*-positive MPN in patients with new SVTs, routine screening with *JAK2V671F* mutation was warranted in all patients presenting with idiopathic SVTs, even in patients where MPN phenotype is masked.[38,39] Risk factors associated with presentation of BCS as a consequence of MPN appear to be *JAK2V617F* positivity, PV, and, paradoxically, for thrombosis risks in general, female sex, and younger age (Table 2).

PV may run a course of uncomplicated disease requiring only phlebotomy for decades, or may follow a progressive, malignant course similar to CML in which a relatively short polycythemic phase is followed by transformation to MF (PPVMF) and then to AML, all occurring within a matter of years from the original PV diagnosis. The PPVMF phase of the disease clinically and molecularly resembles de novo PMF, with high stem cell JAK2 allele burdens and the association of chromosome changes such as 20q deletion, 13q deletion, trisomy 9, and mutation of the *ASXL1* gene.[40-42] The nonrandom chromosomal changes that are present in greater than 60% of patients with PPVMF, and their similar prevalence in de novo PMF, suggests that these lesions drive MF physiology and alter the cellular context of JAK2V617F signaling.[43] Recent studies of PPVMF indicated that approximately 15% of patients developed MF at a median of 10 years after PV diagnosis and that this percentage increased to almost 50% after 20 years. These studies also found that a subset of patients with PV who had lower JAK2V617F allele burdens had a significantly lower risk for this outcome compared with the subset of patients with higher allele burdens (Table 3).[44,45]

AML occurring directly out of chronic phase PV is unusual and estimated to occur in as many as 4% of patients with PV; whereas, AML evolving from PPVMF is more common, occurring in as many as 20% of patients with MF.[46] The leukemia-accelerating effects of radioactive phosphorus and the alkylator pipobroman on the natural history of PV is uncontested.[24,47] Moreover, this experience in PV calls any potentially genotoxic therapy into question regarding safety, especially given the long-term exposure to any therapy that some patients with PV will require, and the need for therapy in older patients with PV, where genomic integrity is an issue. Traditional risk factors for AML development include older age, P32 or alkylator therapy, PPVMF, and hemoglobin less than 10 g/dL.[47]

Myelofibrosis

It has long been noted that patients with MF experience markedly different outcomes.[48,49] To better understand and quantitate this phenomenon, a methodical approach to analyzing risk factors associated with higher-risk disease has resulted in the birth of several clinically useful scoring systems that incorporate clinical and laboratory findings in the patient with MF. Cervantes et al examined 1,054 patients with PMF.[50] In this study, the multivariate analysis demonstrated that five risk factors were significantly associated with determination of prognostic score when assessed at time of MF diagnosis: (1) age older than 65 years, (2) leukocytosis (WBC greater than 25 K/uL), (3) circulating blasts of 1% or greater, (4) presence of constitutional symptoms, and (5) anemia of hemoglobin less than 10 g/dL. This divided the patients into groups of low-risk, intermediate-1, intermediate-2, and high-risk, with median overall survivals of 135 months, 95 months, 48 months, and 27 months, respectively. This represents the most widely used scoring system for patients with MF, and, although cytogenetic abnormalities and *JAK2V617* mutation were considered, notably, neither reached independent significance to warrant inclusion in the final scoring system in this original International Prognostic Scoring System (IPSS) model. It is of particular importance that the presence of constitutional symptoms were included and indeed validated in the IPSS model for MF, as this highlights an important part of risk stratification for patients with MPNs: the burden of symptoms experienced in these diseases, even in those patients with lower risk scores, affect not only the quality of life, but also has effects on overall survival outcomes.[51] Several clinical instruments have been developed and validated specifically in patients with MPN, including for patients with MF, to help quantitate and follow these symptom profiles over time.[52,53] These and other widely available instruments will likely continue to be an important part of recording and understanding MPN's risks, comorbidities, and symptoms over time, and be a vital method to reliably follow changes/improvements with disease-modifying agents starting to be used in the clinic.[54]

The IPSS scoring method of risk stratification for patients with MF has had a direct effect on therapeutic investigation and decision making as it helped to select an appropriate patient population for the largest randomized clinical trials testing a novel therapy in patients with MF.[55] On the basis of the IPSS, those patients with intermediate-2 or high-risk MF were included on the original phase III clinical trials testing ruxolitinib, a JAK1/2 inhibitor, against either best available therapy or placebo (COMFORT 1 and 2), thus, identifying the highest-risk/poorest-prognosis patients that might benefit from therapy.[1,6] These trials ultimately led to U.S. Food and Drug Administration approval of ruxolitinib, the first and only therapy specifically approved for patients with MF on the basis of risk stratification, taking into account patient symptom burden and constitutional symptoms into the approval process.[56]

Building on this clinical risk factor model, several other scoring systems for MF have been developed with the aim of providing prognostication for overall survival at any time during disease course, not just at diagnosis, (Dynamic International Prognostic Scoring System [DIPSS])[57] and further refinement with additional risk factors added (DIPSS-plus), including thrombocytopenia, transfusion dependency, and cytogenetic abnormalities.[58] The identification and success-

ful addition of cytogenetic abnormalities to risk stratification for patients with MF recognizes the striking heterogeneity among patients with this disease at the pathobiologic level, reflects the remarkable strides made in these now widely available laboratory assessments, and is in line with prognostic measurement of other myeloid malignancies (MDS, AML) that are all now utilizing cytogenetic analysis as a part of routine risk stratification and treatment decision making.

Besides cytogenetics, it appears that molecular abnormalities may be crucial to understanding the modern risk stratification of the patient with MF.[59] More recent discoveries of the significance of *MPL* and *CALR* mutations added to the already known *JAK2* mutation in diagnosis of MF, however, their significance on risk stratification was unknown until recently.[60] Rumi et al examined the effect of molecular mutations on outcomes in 617 patients with MF. The authors found markedly different outcomes based on the molecular profile: the longest median overall survival was found in *CALR*-mutated (17.7 years), followed by *JAK2*-mutated (9.2 years), *MPL*-mutated (9.1 years), and, finally, a group of patients termed triple-negative (negative for *CALR, JAK2,* and *MPL*) constituted the poorest-prognosis group with median overall survival of only 3.2 years.

Other genetic lesions important in MDS and AML have been identified at a relatively high frequency in MF and may inform risk. For example, mutations in ASXL1 occur in 30% to 36% of patients with MF.[41] Taking some of these newer markers into account, further molecular risk stratification was conducted with inclusion of and assessment of other molecular mutations commonly found in myeloid malignancies that are also found in patients with MF: *IDH, EZH2, SF3B1, SRSF2, U2AF1,* and *ASXL1.*[61] Analyses in large MF cohorts have the power to further refine prognosis based on genetics, with a recent study identifying CALR-negative/ASXL1-positive MF patients exhibiting worse outcomes, suggesting another higher-risk subset.[62]

CONCLUSION

In the 10 years since the discovery of the *JAK2V617* mutation in MPNs, the field has experienced an exponential increase in terms of clinical and basic science research. With improved methods of stratifying risk for patients at the clinical, biologic, cytogenetic, and, now, molecular level, we are entering a new era of recognizing MPN's total burden of disease, and we are beginning to consider assigning targeted treatments based on these assessments. The personalization of MPN diagnosis, prognosis, and treatment will likely include the congruence of clinical factors, formal MPN symptom burden assessment, and cytogenetic and molecular analyses.

Disclosures of Potential Conflicts of Interest

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Current Therapies and Their Indications for the Philadelphia-Negative Myeloproliferative Neoplasms

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OVERVIEW

The groundbreaking discovery of the Janus-associated kinase 2 (JAK2) V617F mutation 10 years ago resulted in an unprecedented intensive basic and clinical research in Philadelphia-negative myeloproliferative neoplasms (MPNs). During these years, many new potential targets for therapy were identified that opened the era of targeted therapy for these diseases. However, only one new drug (ruxolitinib) has been approved during the past 40 years, and, although promising new therapies are evaluated, the armamentarium to treat MPN still relies on conventional drugs, like cytotoxic agents and anagrelide. The exact role of interferon (IFN) alfa still needs to be clarified in randomized studies, although it has been shown to be effective in MPNs for more than 25 years. The current therapeutic strategy for MPNs is based on the risk of vascular complication, which is the main cause of mortality and mortality in the medium term. However, the long-term outcome may be different, with an increasing risk of transformation to myelodysplastic syndrome or acute leukemia during follow-up times. Medicines able to change this natural history have not been clearly identified yet, and allogeneic stem cell transplantation currently remains the unique curative approach, which is only justified for patients with high-risk myelofibrosis or for patients with MPNs that have transformed to myelodysplasia or acute leukemia.

For decades, the armamentarium to treat Philadelphia-negative myeloproliferative neoplasms (MPNs), including polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), was reduced to a small handful of cytotoxic drugs like hydroxyurea (HU); busulfan; and, in some countries, pipobroman.[1] Since the discovery of the JAK2 V617F mutation 10 years ago followed by the discovery of many other genetic alterations,[2] our knowledge of the pathophysiology of these disorders has dramatically changed, with the identification of deregulated crucial signaling pathways like the JAK-STAT (signal transducer and activator of transcription) pathway or mutations affecting the epigenome. With these major advances, MPNs have entered into a new era of targeted therapy, inaugurated with the approval of ruxolitinib, a JAK1/JAK2 inhibitor to treat myelofibrosis (MF)[3,4] and PV.[5]

With conventional therapies, the treatment of MPNs mainly aims at reducing the risk of vascular events (including thrombosis and hemorrhage), which are the main causes of mortality and morbidity over short and medium time periods.[6,7] However, the outcome of patients with these chronic malignancies is different over the long-term evaluations (i.e., after 15 to 20 years of evolution), when transformation to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) becomes a major concern, as demonstrated by the long-term analyses of a randomized study in patients with PV after

more than 16 years of median follow-up time.[8] The development of new therapies raises the hope of new objectives, including reduction of the long-term risk of transformation to MDS or AML; achievement of molecular or histopathologic complete remissions; and, possibly, cure. However, to date, only allogeneic hematopoietic stem-cell transplantation (ASCT) can cure selected high-risk patients with MF.

VASCULAR RISK ASSESSMENT

The evaluation of the risk of vascular complications is a cornerstone of current MPN management, especially in PV and ET. Risk stratification is reviewed in detail in a companion article in this volume (Moliterno and Pemmaraju), and this paragraph will focus on a few elements useful for decision making in MPN therapy. Indeed, in the absence of curative therapy, the aim of this risk-based classification is to avoid the use of cytoreductive therapy in patients who are at low risk of developing thrombosis or hemorrhage. Although many risk factors have been assessed and have had some relevance in retrospective studies, the most reliable parameters remain very easy to collect: age and history of vascular events. Patients younger than age 60 and without any previous thrombosis or bleeding related to their MPN are at low risk of developing vascular complications. In contrast, patients with one or both these features are at high vascular risk and will benefit from cytoreductive therapy.

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Scores predicting overall survival in PV and ET also are available; however, considering the long survival of these patients, they currently are not used for therapeutic choices.[9,10] In contrast, in PMF, the overall median survival being is 6 years, and the relevant endpoint for prognostication is survival. The International Prognostic Scoring System (IPSS)[11] is used at diagnosis to distinguish four risk categories (low, intermediate 1, intermediate 2, and high risks). This system has been refined further by the development of the dynamic IPSS (DIPSS),[12] which may be used at any time during follow-up periods, and the DIPSS-plus score,[13] which incorporates thrombocytopenia, transfusion requirements, and cytogenetics. The role of *CALR*[14,15] and other mutations (i.e., *EZH2, ASXL1, SRSF2, IDH1/2* mutations), which comprise a high molecular risk category in PMF,[16] has been underscored but has yet to be incorporated in a new prognostic model.

TREATMENT OF POLYCYTHEMIA VERA

PV therapy must address both short- and long-term objectives. In the short term, therapeutic aims are to reduce the risk of occurrence and recurrence of thrombosis, first via reduction of the hematocrit—a simple parameter reflecting blood viscosity. However, although very simple to use and reliable, hematocrit is not the unique suspect, and many other abnormalities play a role in the occurrence of thrombosis in patients with PV. Quantitative but also qualitative abnormalities (with features of aberrant activation) of leukocytes, platelets, and even red cells have been reported to take part in the prothrombotic state of patients with PV (and, more generally, with MPN).[17,18] Finally, general cardiovascular risk factors (e.g., smoking, hypertension, diabetes, dyslipidemia) should not be neglected and require a particularly careful evaluation in patients with PV, because thrombosis is often multifactorial and caused by an accumulation of adverse factors. A strict control of these standard risk factors, therefore, is a major component of successful PV therapy.

Regardless of their risk category, treatment recommendations[1] for all patients with PV include antiplatelet therapy with low-dose aspirin (100 mg/day) and phlebotomy to maintain a hematocrit less than 45%. Patients who are age 60 or older and/or who have a history of thrombosis are high-risk patients and should receive cytoreduction with HU or recombinant IFN-alfa. HU is the preferred option for high-risk patients in many countries where the off-label use of IFN-alfa is not possible (Table 1).

First-Line Therapy

Phlebotomy can be an emergency therapy at diagnosis, in patients who present with very high hematocrit and clinical signs of hyperviscosity, as well as a long-term maintenance therapy to control the hematocrit in low-risk patients.[19] The optimal target of hematocrit levels was a matter of debate, but a recent multicenter, randomized clinical trial (Cyto-PV) showed that a hematocrit maintained strictly at less than 45% during follow-up periods was significantly associated with a lower incidence of thrombosis (p = 0.007).[19] Low-dose aspirin is the second cornerstone of PV therapy, because it has been shown in a large European, double-blind, placebo-controlled, randomized trial (the ECLAP study) to significantly reduce a primary combined endpoint that included cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and major venous thromboembolism.[6]

In addition to this strategy, a cytoreductive drug should be prescribed in high-risk patients with PV (i.e., age older than 60 and/or with a history of a vascular event). The European LeukemiaNet (ELN) recommendations for the management of PV suggested that HU and IFN-alfa were the cytoreductive treatments of choice as first-line therapy for high-risk patients with PV.[1] HU is a well-known drug with good efficacy and tolerance in the majority of patients. This efficacy is often

KEY POINTS

- Therapy for myeloproliferative neoplasms currently is based on the risk for vascular complications (thrombosis and hemorrhage) and requires a strict control of other well-known cardiovascular risk factors (e.g., smoking, hypertension, diabetes, dyslipidemia).
- Phlebotomy to maintain the hematocrit less than 45% and low-dose aspirin are the cornerstone of therapy for polycythemia vera, although patients older than age 60 or who have a history of thrombosis (i.e., high-risk patients) should receive a cytoreductive agent.
- First-line therapy for high-risk polycythemia vera includes hydroxyurea or interferon alfa, whereas ruxolitinib has been approved recently for patients whose disease is resistant to or who are intolerant to hydroxyurea.
- Patients with essential thrombocythemia may receive low-dose aspirin plus hydroxyurea when they are at high risk. Anagrelide often is preferred as second-line therapy, whereas interferon alfa also may be useful in subgroups of patients.
- Treatment of myelofibrosis is often symptom driven, and ruxolitinib currently is the treatment of choice in patients with intermediate- or high-risk disease who have symptomatic splenomegaly and disabling symptoms.

TABLE 1. Risk-Based Therapy of Polycythemia Vera and Essential Thrombocythemia

Risk-Based Treatment Group	PV	ET
All Patients	Management of cardiovascular risk factors	
Low-Risk Patients	Aspirin	Aspirin
	Phlebotomy	
High-Risk Patients		
First line	HU or IFN-alfa	HU
Second line	Switch IFN-alfa or HU	Anagrelide
	Ruxolitinib	
Other	Busulfan	IFN-alfa

Abbreviations: PV, polycythemia vera; ET, essential thrombocythemia; HU, hydroxyurea; IFN, interferon.

maintained in the long-term period, although skin toxicity and secondary resistance may develop over time and may lead to treatment discontinuation in 10% to 20% of patients.[5] Another issue for patients with PV in the very long-term period is the risk of disease transformation. In the unique randomized trial comparing HU with another cytoreductive drug (pipobroman) in PV, the cumulative incidence of AML and MDS at 10, 15, and 20 years was 6.6%, 16.5%, and 24%, respectively, in the HU arm and 13%, 34%, and 52%, respectively, in the pipobroman arm.[8] Other studies from registry data and from a prospective analysis with a shorter follow-up time failed to attribute a clear leukemogenic risk to HU.[20,21] Overall, there is no definitive evidence for (or against) a leukemogenic risk of HU, but it should be emphasized that this risk may appear after prolonged exposure to this drug. Thus, it seems reasonable to adopt a conservative approach and to consider alternative treatments in young patients and in those previously treated with other myelosuppressive agents.

IFN-alfa has been shown to induce a high rate of hematologic response and to significantly reduce the malignant clone, as shown by the percentage of JAK2 V617F-mutated alleles in independent phase II studies.[22-24] In selected patients, complete hematologic, molecular, and histopathologic remissions were observed, suggesting a possible impact on the natural disease history. IFN-alfa has never been suspected to be leukemogenic, which is another potential property favoring its use in younger patients.[25] The main toxicity and contraindications for IFN-alfa are well known because of the wide use of this drug in patients with viral hepatitis. Overall, approximately 20% to 30% of patients have to discontinue therapy with pegylated forms of IFN-alfa for toxicity reasons.[26] However, this drug (in any of its various presentations) is not approved for the treatment of PV. Two important ongoing, prospective, randomized clinical trials comparing pegylated forms of IFN-alfa with HU in high-risk patients with PV should provide the critical information needed to determine the exact role of IFN-alfa in this setting (NCT01259856 and NCT01949805).

Patients with PV may experience a broad-ranging symptom burden that includes fatigue, pruritus, and painful splenomegaly.[27] The combined symptom burden experienced by some patients with PV is associated with reductions in quality of life (QoL). Among these symptoms, aquagenic pruritus may be a disabling symptom in some patients with PV; JAK inhibitors and IFN-alfa are the best options to treat this symptom. Other nonspecific choices that may be helpful include antihistamines, selective serotonin-reuptake inhibitors, and PUVA (psolarens plus ultraviolet A) therapy.[28,29]

Second-Line Therapy

The choice of second-line myelosuppressive drugs for PV should be evaluated carefully, because some drugs administered after HU may enhance the risk of AML.[30] Therefore, one may switch drugs between HU or IFN-alfa when used as first line (Table 1).

Very recently, the JAK1/JAK2 inhibitor ruxolitinib was evaluated in patients with PV who were intolerant of or resistant to HU in a phase III, randomized trial versus the best available therapy (NCT01243944).[5] The primary endpoint was a composite of hematocrit control and a 35% or greater reduction in spleen volume at week 32. This endpoint significantly favored ruxolitinib, having been met by 21% of patients in the ruxolitinib arm versus 1% in the standard therapy arm (p < 0.0001). In addition, a greater proportion of patients receiving ruxolitinib achieved complete hematologic remission and experienced a significantly better improvement of PV-related symptoms. Overall, ruxolitinib was tolerated by most patients; 85% of patients randomly assigned to ruxolitinib remained on treatment after a median follow-up time of 81 weeks. The most frequent grade 3 or 4 adverse events reported by patients receiving ruxolitinib were thrombocytopenia (5.5%), dyspnea (2.7%), anemia (1.8%), and asthenia (1.8%). Other adverse events of interest included herpes zoster infection, which was observed in 6.4% of patients in the ruxolitinib arm (all grade 1 or 2), and non-melanoma skin cancer, which occurred in four (3.6%) patients. Based on the results of this study, ruxolitinib was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with PV who have had an inadequate response to or are intolerant of HU, and it is a clear new option for second-line therapy in these patients.

In selected patients, alkylating agents like busulfan may still be useful when other drugs have failed or are contraindicated, although they may increase the leukemogenic risk.[1]

TREATMENT OF ESSENTIAL THROMBOCYTHEMIA

In contrast with PV, the potential benefit of aspirin therapy has never been assessed in a randomized, controlled trial in ET. In addition, there is a concern that bleeding is a particular risk for patients with ET who have extreme thrombocytosis (greater than $1,500 \times 10^9$/L) because of acquired von Willebrand disease.[31] Considering these uncertainties, low-dose aspirin remains recommended for high-risk patients with ET who do not have a clear contraindication to this drug.[1] For patients with low-risk ET, a retrospective analysis suggested that only patients with the JAK 2V617F mutation or those who have cardiovascular risk factors might benefit from antiplatelet therapy.[32] However, on the basis of currently available data, it seems reasonable to use low-dose aspirin for low-risk patients with ET, because thrombosis remains the major clinical hazard. This indication is clearly evident in patients who experience microvascular disturbances.[1] Conversely, the presence of extreme thrombocytosis (greater than $1,500 \times 10^9$/L) temporarily contraindicates the use of antiplatelet agents, a therapy that can be started after reduction of the platelet count with cytoreductive drugs.

Regarding the choice of the first-line cytoreductive therapy for high-risk patients with ET (Table 1), recommendations can be based on three randomized trials.[33-35] HU significantly reduced the rate of thrombosis in high-risk patients with ET versus no myelosuppressive therapy,[33] showing that these patients should receive a cytoreductive drug and not only antiplatelet agents. The use of anagrelide versus HU has been evaluated in two studies: the PT-1 study and the noninferiority ANAHYDRET study. Anagrelide was equivalent to HU

in reducing platelet counts in both studies. In the PT-1 study, an excess of arterial thrombosis was observed in the anagrelide arm compared with HU.[34] However, in the ANAHYDRET study that included patients with ET who were strictly diagnosed using World Health Organization criteria (including a bone marrow biopsy in all patients to rule out early phases of myelofibrosis), study equivalence was reported.[35] Based on these results, HU and low-dose aspirin combined is often the recommended first-line therapy for high-risk patients with ET,[1] but anagrelide also may be appropriate in specific subgroups of patients. Of note, in the absence of ischemic symptoms or vascular complication, platelet reduction should be progressive over a few weeks with increasing doses of cytoreductive drugs to avoid the occurence of thrombocytopenia or leukopenia.

The role of IFN-alfa therapy in ET needs to be clarified, although many small, phase II studies have shown that this drug also was very efficient to control thrombocytosis.[26] In addition, it has been shown that IFN-alfa was able to induce molecular responses by reducing the mutant allele burden in patients harboring mutations in JAK2[23] or in *CALR*[36] genes. Whenever possible, patients with ET should be enrolled in randomized studies evaluating HU compared with IFN, like the ongoing MPD-RC 112 study (NCT01259856). Anagrelide may be used as second-line therapy for patients who are resistant to or intolerant of HU. IFN-alfa and busulfan also are possible options in this setting. The use of cytotoxic agents, in the youngest patients or, especially, in combination should be avoided when possible, and IFN-alfa or anagrelide could be the best options in these situations.

TREATMENT OF MYELOFIBROSIS

Because there is no curative therapy other than ASCT for myelofibrosis, treatment basically is palliative and usually is guided by the principal disease manifestation.

Anemia

Of note, no drug has approval for this particular indication. A hemoglobin of less than 10 g/dL, which is an adverse prognostic factor, usually prompts consideration of treatment, although this threshold obviously is subject to adaptations depending on age and comorbidities. One option is the use of erythropoiesis-stimulating agents, which have been reported to improve anemia in 25% to 50% of patients.[37,38] Patients who have low endogenous erythropoietin levels (less than 125 mU/mL) may be the best candidates for this therapy, whereas patients who have major splenomegaly or transfusion dependence are unlikely to experience clinically relevant improvement. Androgens also have reportedly improved anemia in a similar proportion of patients. In this class of drugs, danazol is the treatment of choice, inducing similar results with less toxicity at the recommended dose of 400 mg to 600 mg daily maintained for at least 6 months, then progressively reduced to the minimum necessary for maintenance. Immunomodulating agents also may be useful in managing MF-related anemia. Low-dose thalidomide or low-dose

lenalidomide, combined for the induction treatment with prednisone, provide a 20% to 30% response.[39,40] Of note, lenalidomide as a single agent is the treatment of choice for patients with MF who have a 5q deletion.[41] Corticosteroids alone sometimes may be helpful and provide a modest benefit for patients resistant to the above-mentioned therapies, especially if a hemolytic part can be demonstrated. Last, splenectomy can be useful in patients who have transfusion-dependent anemia that is refractory to any therapy,[42] but it needs careful evaluation because of the risks of complication.

Splenomegaly and Other Sites of Extramedullary Hematopoiesis

Usually, treatment of splenomegaly is not necessary per se, at least until the onset of associated symptoms. HU used to be the first-line therapy for symptomatic splenomegaly, and approximately 40% of patients experienced a reduction in spleen size.[43] However, HU efficacy is usually modest (spleen size diminishing only of a few centimeters) and not durable; published experience suggests that the majority of patients need an alternative treatment after a median time of 12 months. HU currently is clearly superseded by JAK inhibitors in this indication. Splenectomy is sometimes required in patients who have large and painful splenomegaly that is refractory to medical therapy.[42] Splenectomy requires an experienced surgical team and critical care support to minimize the risks associated with the procedure, because mortality and morbidity rates of 5% to 10% and 25%, respectively, have been reported in a large, single-center experience.[42] Splenic irradiation is another alternative treatment of refractory and symptomatic splenomegaly.[44] However, this treatment should be used with caution (fractionated, low dose) because of a high risk of severe cytopenias. In addition, the benefit is only transient. In contrast, low-dose radiation is the therapy of choice for symptomatic extramedullary hematopoiesis in sites other than the spleen and liver (e.g., skin, central nervous system).[45]

The Role of JAK Inhibitors

This new class of drugs clearly has changed our management of MF for a significant proportion of patients and has provided unanticipated benefits. These drugs were designed to target the dysregulated JAK-STAT signaling pathway, a typical feature of patients with MPN independent of the presence of the JAK2 V617F mutation. Better knowledge of the complexity of the mutational landscape of MPNs clearly demonstrates now that the story of these drugs will not be similar to that of tyrosine kinase inhibitors in chronic myeloid leukemia. In addition, currently available JAK2 inhibitors are not selective for the mutant form and, thus, inhibit wild-type JAK2 signaling as well (explaining the on-target hematologic toxicity usually observed with these agents). To date, only ruxolitinib, the first-in-class oral JAK1/JAK2 inhibitor, has been approved for MF treatment. Two independent, phase III studies have shown significant efficacy of ruxolitinib to reduce splenomegaly and improve symptoms compared with placebo (COMFORT-1 study)[4] or the best available therapy (COMFORT-2 study).[3] These benefits usually occur within a few days after ruxolitinib initiation and are durable

throughout therapy, but they are strictly drug and dose dependent; a reduction in the dose will rapidly result in a slight re-increase in spleen size, whereas discontinuation of the drug will lead to a return of signs and symptoms to their baseline levels within a week. Of note, sudden ruxolitinib withdrawal has been reported to potentially induce severe complications, like shock-like syndrome, because of the re-emergence of the suppressed inflammatory cytokines.[46] Although such dramatic adverse events have not been observed in the two COMFORT phase III studies, abrupt interruption should be avoided, and withdrawal of the drug should be tapered. Thrombocytopenia is a frequent adverse event observed with ruxolitinib (contraindicated in patients who have platelet counts less than 50×10^9/L), and it requires dose adaptation but very rarely drug discontinuation. New onset or worsening of anemia also can be anticipated when ruxolitinib therapy starts, especially during the first 3 to 6 months of therapy. This drug also is associated with an increased risk of infection, which requires patient counseling and sometimes prophylactic measures (as reviewed by Heine et al[47]).

A survival advantage for patients treated with ruxolitinib was first shown from an historic comparison with matched MF populations.[48,49] Extended follow-up evaluation of the phase III studies indicated a survival advantage for patients who received ruxolitinib.[50] However, there is still little evidence of a disease-modifying effect, although case reports suggest that reduction in JAK2 mutant allele burden and bone marrow fibrosis can be achieved with the long-term use of ruxolitinib in selected patients.[51]

Other JAK inhibitors currently are being evaluated in clinical studies, but several clinical development programs have been terminated because of emergent toxicity, in particular neurologic toxicity, with some of these drugs.[52] Among JAK inhibitors currently being tested in phase III studies, pacritinib may have the peculiarity of a lack of toxicity on the megakaryocytic lineage that allows its use in patients with thrombocytopenia.[53] Momelotinib, despite its potent anti-JAK2 activity, may have a positive impact on the anemia of transfusion-dependent patients.[54] However, these potentially useful properties for subgroups of patients with MF who have these two unmet needs have to be confirmed in the ongoing phase III studies.

The Role of Stem-Cell Transplantation for Myelofibrosis in the Era of JAK Inhibitors

The role of ASCT has decreased dramatically in chronic myeloid leukemia since the advent of tyrosine kinase inhibitors, but the situation is not yet comparable in classical MPNs. ASCT currently remains the only curative treatment approach for myelofibrosis, which results in resolution of bone marrow fibrosis, molecular remission, and restoration of nonmalignant hematopoiesis.[55,56] Overall, in recent series, approximately 40% to 70% of patients may have been cured with ASCT,[55,56] but transplant-related mortality is not negligible and justifies careful patient selection. Of note, patients with chronic-phase PV or ET are not eligible for ASCT, a situation that changes when their disease progresses into MF or

secondary AML.[57] The best candidates for ASCT are high-risk patients with MF (intermediate 2 and high-risk categories according to IPSS), the limit of age being discussed according to conditioning intensity.[1] The use of ruxolitinib before transplantation with the objective of spleen size reduction in patients who have massive splenomegaly (to avoid pretransplantation splenectomy) and to improve general performance status is evaluated in prospective studies and should, therefore, be considered presently as experimental. In patients with massive splenomegaly, pre-transplant splenectomy should be discussed to improve engraftment and transplant outcome.[55–57]

MPN THERAPY DURING PREGNANCY

The treatment of patients with MPN during pregnancy is a nonexceptional challenge in clinical practice, in particular considering that there is a peak incidence of ET in young women. Pregnancy in MPN clearly is possible in the majority of patients, and the disease, per se, is not a contraindication. However, loyal information about the risks of complications should be provided, and the project of pregnancy should be prepared in close collaboration among the patients, the hemato-oncologist, and a specialized obstetrical team used to manage high-risk pregnancies. Available data about pregnancies in ET and PV mainly are retrospective and, therefore, possibly biased; randomized or controlled studies do not exist in such patients. During pregnancy, similar types of complications have been observed in both ET and PV (with different incidences), and the overall success rate of pregnancy was approximately 60% to 70%. None of the drugs useful to treat MPNs has a license for use during pregnancy. However some recommendations have been produced.[58] Patients should be screened for thrombophilia, an additional risk factor for complication that may change the management (with the use of heparin). HU and anagrelide should be stopped before conception, with a washout period of several weeks whenever possible. Low-dose aspirin should be continued (or started) and maintained throughout the pregnancy, relayed by low-molecular-weight heparin (easier to manage in case of bleeding complications) a couple of weeks before delivery. In patients with PV, phlebotomy can usually help control the hematocrit if needed. In patients with ET, if cytoreduction is necessary, IFN-alfa can be proposed.[25] Close fetal monitoring (including echography and Doppler) should be planned, especially during the last trimester, which is a period of high risk for placental vascular complications. Blood counts of the mother in the postpartum period should be monitored carefully, because a rebound in platelet counts can be observed within few days after delivery, which is a period of high risk for thrombosis that should be prevented by the use of a low-molecular-weight heparin for up to 6 weeks after delivery.[58]

THE FUTURE OF MPN THERAPY

One possible avenue for MPN therapy is the development of personalized medicine. Indeed, among cancers, MPNs could be

ideal candidates for such strategy. There is evidence to show that the mutational profile found in hematopoietic cells has an influence on treatment efficacy. For example in ET, patients with or without a JAK2 mutation display different responses to HU, and the control of the platelet count requires lower doses of HU in patients who are positive for JAK2 V617F.[59] In addition, a reduced prevalence of arterial thrombosis was observed in patients with a JAK2 V617F–positive status who were receiving HU compared with anagrelide, whereas no difference was found in patients with a JAK2 V617F–negative status for the same endpoint. In PV, IFN-alfa had a differential impact on malignant clones according to the presence of JAK2 or TET2 mutations; the JAK2-mutated clones were much more sensitive to IFN-alfa than the clones with the TET2 mutation.[60] These findings suggest that the mutational profile could provide important information not only in terms of prognosis but also for the choice of therapy. This could be particularly important in patients with MF, because they have a poorer life expectancy and often-complex mutational profiles. To validate such a personalized approach, there is a need for prospective studies in cohorts of patients fully characterized for mutations that may change the response to therapies. This characterization could be available soon in a number of centers with the rapid development and wider availability of next-generation sequencing techniques.

In terms of new therapies, two classes of drugs currently are being evaluated in early-phase studies and may play a role in MPN management in the future. First, histone deacetylase inhibitors have shown some efficacy, like panobinostat in PMF[61] or givinostat in PV.[62] The most promising results with these drugs may result from a combination with JAK inhibitors by targeting parallel signaling pathways involved in disease development. A telomerase inhibitor, imetelstat, also has had efficacy in ET and PMF and currently is being evaluated for efficacy and safety.[63]

Disclosures of Potential Conflicts of Interest

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LEUKEMIA, MYELODYSPLASIA,
AND TRANSPLANTATION

Translating Knowledge into Therapeutic Progress in Myelodysplastic Syndromes

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Myelodysplastic Syndromes and Myelodysplastic/Myeloproliferative Neoplasms: An Update on Risk Stratification, Molecular Genetics, and Therapeutic Approaches Including Allogeneic Hematopoietic Stem Cell Transplantation

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OVERVIEW

Myelodysplastic syndromes are a heterogeneous group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, peripheral cytopenias, and a variable propensity for leukemic transformation. In recent years there has been an explosion of information on the molecular genetic changes underlying these disorders. This information has substantial prognostic implications, and the influence on therapeutic approaches and the treatment of patients is evolving. Allogeneic hematopoietic stem cell transplantation (alloSCT) is the only known cure for these diseases, but appropriate patient selection is of utmost importance from a risk-benefit perspective. This review focuses on the factors influencing risk stratification in MDS and optimal choice of front-line therapy in the current era, including the interplay of clinical factors and molecular genetic factors, and factors that determine eligibility for alloSCT. The myelodysplastic/myeloproliferative diseases also will be discussed, including the increasing effort to understand the molecular genetics and natural history of these disorders and treatment approaches.

The myelodysplastic syndromes are a clinically and molecularly heterogeneous group of clonal stem cell disorders with management options ranging from observation and growth-factor therapy to more intensive approaches, such as hypomethylating agent (HMA)–based therapies, intensive induction chemotherapy, and alloSCT.[1] During the last decade, rapid developments centered around high-throughput molecular technologies have resulted in remarkable advancement toward the understanding of MDS pathogenesis.[2-6] These technologies are anticipated to translate to innovative targeted agents that will radically affect the natural history of this disease. Presently, however, alloSCT remains the only curative treatment option in patients with MDS.[2,7-9] Even if substantially reduced during the last 20 years, mortality and morbidity risks associated with alloSCT continue to represent a major limit to the feasibility of such a therapeutic strategy in the large number of patients.[8,10,11] Therefore, the accurate selection of patients—together with optimal timing of transplantation—represent critical issues for maximum improvement of the alloSCT risk-benefit ratio in MDS.

As such, important advancements have been made toward the dissection of MDS clinical heterogeneity that have incorporated both clinical and molecular characteristics. In this review, we will discuss recent refinements to prognosis for patients with MDS based on clinical, cytogenetic, and molecular risk factors. We also will discuss the approach to the selection of front-line therapy in MDS, including a particular focus on alloSCT. Lastly, we will highlight myelodysplastic/myeloproliferative neoplasms (MDS/MPNs), including recent insights into the molecular genetics and emerging therapeutic approaches in patients with these diseases.

PROGNOSTIC STRATIFICATION IN MYELODYSPLASTIC SYNDROMES

MDS is a disease found in older adults, with a median age at diagnosis of age 71. The estimated 3-year survival rate of patients with MDS is 45%,[12] although there is substantial variability in outcomes even within the same French-American-British (FAB)[13] classification system and the more recent World Health Organization (WHO) morphologic subtypes.[14] This heterogeneity in outcomes underscores the need for accurate prognostication and has fuelled the evolution of various prognostic scoring models.

Prognostic Classification Models

The international prognostic scoring system (IPSS), a widely validated system currently in use, originally was created from data from 816 patients. The IPSS encompasses karyotype, blast percentage, and the number of cytopenias, thus stratifying patients with de novo MDS into four risk categories. These include lower risk MDS comprising low and intermediate-1 risk categories, and higher risk MDS comprising intermediate-2 and high-risk categories; with median survivals ranging from 5.7 to 0.4 years.[15]

Limitations associated with the IPSS include the lack of consideration of the severity of cytopenias, and transfusion dependency; underweighting of the prognostic import of karyotype relative to marrow blast–percent; and the fact that this model is applicable only at diagnosis. Several of these limitations were addressed by the development of other models, including the WPSS,[16] which incorporates transfusion dependency and WHO subtype, among other factors. It is a dynamic model that can be applied at diagnosis and follow-up. The University of Texas MD Anderson Cancer Center (MDACC) prognostic model includes a broader population of patients, such as patients with therapy-related MDS and patients with chronic myelomonocytic leukemia (CMML).[17] An additional prognostic model focused on lower-risk disease (LR-PSS) has been developed at MDACC.[18]

The revised IPSS (IPSS-R),[19] which was created from an evaluation of more than 7,000 patients, incorporates a comprehensive 5-tiered cytogenetic risk stratification system that comprises 15 cytogenetic subtypes (Table 1).[20] It also accounts for the degree of cytopenias and provides a more discriminant assessment of bone marrow– blast percentage. The predictive value of cytogenetics in MDS has long been recognized, and the comprehensive cytogenetic strata included in the IPSS-R assure that chromosomal aberrations of prognostic importance are accorded appropriate weight in the model relative to bone marrow blast–percent. Five risk groups are

identified—very low, low, intermediate, high, and very-high with median survival ranging from 8.8 to 0.8 years.

Similar to the IPSS, the IPSS-R was generated on data from patients evaluated at diagnosis and censored at the time of receipt of disease-modifying therapy. Despite these issues, the IPSS-R has been rapidly validated by several groups to be more discriminant than the IPSS and the WPSS,[21] and to retain its predictive value even in patients treated with disease-modifying agents.[22,23] Therefore, in just a few short years since its introduction, IPSS-R is rapidly being adopted as the preferred clinical prognostic tool for risk stratification in MDS.

The Evolving Role of Molecular Genetics on Risk Prediction

A comprehensive evaluation of the prognostic relevance of point mutations in refining risk stratification in MDS was first established in a study of 439 patients with MDS.[24] Using next-generation DNA sequencing and mass spectrometry genotyping to evaluate 111 genes, mutations in five genes (*TP53, EZH2, ETV6, RUNX1,* and *ASXL1*), which collectively occurred in approximately one-third of patients, were found to confer poor risk prognosis, independent of established clinical risk factors such as IPSS. Within each IPSS subgroup, the presence of one or more of these mutations was demonstrated to result in a decline in overall survival, which approximated that of the next-highest IPSS risk group.[24]

The same group has since validated the prognostic effect of these mutations (*EZH2, RUNX1, TP53,* and *ASXL1*) in patients with lower-risk MDS. The presence of these mutations was found to be associated with a shorter overall survival independent of the LR-PSS.[25] In a multivariate analysis that included LR-PSS and other mutations, only *EZH2* mutations retained independent prognostic significance. The clinical implication of upstaging for the risk group is recognition that patients in lower-risk IPSS categories have a worse prognosis, which may result in consideration of more intensive treatment approaches for such patients.[24,26]

It is now evident that more than 40 genes are mutated in MDS.[4,27-29] Approximately 90% of patients with MDS harbor at least one mutation, with a median of two or three mutations detected per patient (range, 1 to 12). Mutations could be categorized into subgroups that affect specific functional pathways (Fig. 1), including the spliceosome machinery (*SF3B1, SRSF2, U2AF1, U2AF2, ZRSR2*); DNA methylation (*TET2, DNMT3A, IDH1, IDH2*); chromatin modification (*ASXL1, EZH2*); RAS and other kinase signaling pathways (*NRAS, KRAS, CBL, JAK2*); transcription factor (*TP53, RUNX1, EV1, GATA2*); cohesin; and DNA repair pathways. Of these, mutations affecting RNA splicing and epigenetic dysregulation (DNA methylation and chromatin modification) were commonly observed, underscoring the critical importance of these pathways in MDS pathogenesis. In particular, more than 50% of patients had a mutation in a component of the spliceosome machinery, identifying prem-RNA splicing as the most frequently altered biologic pathway in these diseases.

TABLE 1. MDS Cytogenetic Risk Stratification System

Risk Group	Frequency (%)	Karyotypic Abnormalities	Median Survival (y)	Time until 25% of Patients Developed AML (y)
Very good	4%	-Y, del(11q)	5.4	NR
Good	72%	Normal, del(5q), del(12p), del(20q), double including del(5q)	4.8	9.4
Intermediate	13%	Del(7q), +8, +19, i(17q), any other single or double independent clones	2.7	2.5
Poor	4%	-7, inv (3)/t(3q), double including -7/del(7q), complex with 3 abnormalities	1.5	1.7
Very poor	7%	Complex (> 3 abnormalities)	0.7	0.7

Abbreviations: MDS, myelodysplastic syndromes; y, years; AML, acute myeloid leukemia; NR, not reported.

These studies also provided several additional insights into the role of the molecular genetic profile in determining clinical and phenotypic heterogeneity associated with the disease. For example, the high frequency (75%) of *SF3B1* mutations in MDS subtypes associated with ring sideroblasts was confirmed, implying that this mutation is a significant predictor for the presence of ringed sideroblasts in the marrow. Only mutations in *SF3B1* were associated with a better clinical outcome. In contrast, the average number of mutations was higher per patient in the higher-risk WHO morphologic categories (i.e., refractory anemia with excess blasts (RAEB1 and RAEB-2), which is consistent with a higher degree of clonal evolution in these subtypes). Leukemia-free survival in patients with MDS was found to negatively correlate with the combined number of oncogenic and cytogenetic lesions. The number ranged from 49 months in patients with one lesion to 4 months in patients with six or more mutations. Furthermore, the number of oncogenic mutations provided independent prognostic information after stratification by the IPSS.[4]

Insights into clonal evolution and clonal architecture of MDS also have been obtained from studies[4,30] with mutations in genes involved in RNA splicing or epigenetic regulation with a higher variant allele fraction, which suggests that these mutations occurred earlier during clonal evolution. Both clonal and subclonal events within the same genes, however, retained similar prognostic significance. This suggests that the finding of a mutation in a minor subclone is clinically relevant, thus emphasizing the potential utility of a targeted deep-sequencing approach that is sensitive enough to detect minor subclonal events.

Mutations within the same functional pathways often were mutually exclusive (e.g., *TET2* and *IDH1/2* mutations, which both affect DNA hydroxymethylation). Similarly, mutations involving the spliceosome machinery rarely co-occur. Biologically relevant interactions also were found in patterns of co-occurrence. For example, *SF3B1,* which is associated with good prognosis, was mutually exclusive with *ASXL1* and *IDH2,* which both confer a poor prognosis. However, *SRSF2* showed a clear propensity to associate with *TET2* and its co-mutation is highly associated with monocytosis.[4,27,31] It is plausible that such biologic insights also will be of clinical value in the design and use of targeted therapies.

These molecular profiling efforts successfully demonstrate that the integration of clinical, morphologic, and cytogenetic information already encompassed by the IPSS and IPSS-R, along with the comprehensive molecular genetic profile now available via targeted deep sequencing techniques, has the potential to substantially refine risk stratification in MDS.[27] In the 21st century, it is highly anticipated that such combined risk models—once validated prospectively—will enter into common clinical use to refine prognosis and potentially determine treatment approaches for patients with MDS.

FIGURE 1. The Mutational Complexity of MDS

- RNA Splicing ~ 64%
- DNA methylation~45%
- Chromatin modification ~27%
- Transcription factor~15%
- Receptors/Kinases~15%
- RAS pathway~12%
- DNA repair~10%
- Cohesin~13%
- Other~10%
- No mutation~10%
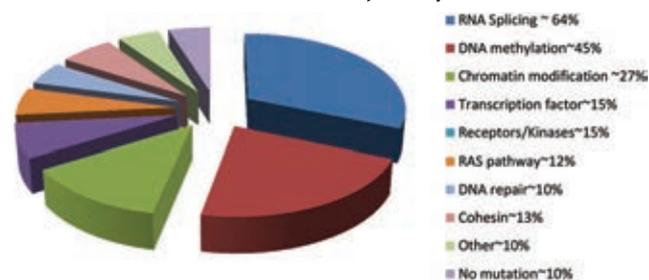
This chart illustrates the mutational complexity of MDS, with mutations organized into functional pathways affecting RNA splicing (includes: *SF3B1, SRSF2, ZRSR2, U2AF1/2*); DNA methylation (includes *TET2, DNMT3A, IDH1/2*); chromatin modification (includes *ASXL1, EZH2*); transcription factor (includes *RUNX1, TP53, BCOR, PHF6, NCOR, CEBA, GATA2*); receptors/kinases (*JAK2, MPL, FLT3, GNAS, KIT*); RAS pathway (*KRAS, NRAS, CBL, NF1, PTPN11*); DNA repair (*ATM, BRCC3, DLRE1C, FANCL*); and cohesins (*STAG2, CTCF, SMC1A, RAD21*). In approximately 10%, no mutation could be identified. Overlapping mutations (co-occurrence of two or more mutations in patients with MDS) are not depicted on this chart, thus percentages add up to more than 100%. Chart is created from data derived largely from targeted deep sequencing of 104 genes in a cohort of 944 patients with MDS, published by Haferlach et al.[27]

FRONT-LINE THERAPY IN MYELODYSPLASTIC SYNDROMES

The concept of individualized therapy is particularly relevant in the selection of optimal therapeutic strategies in this disease, and it should incorporate a consideration of both patient- and disease-specific elements. Higher-risk patients generally are offered more intensive therapeutic options, including HMA therapy and an early consideration of stem cell transplantation, which is discussed in substantial detail below. Lower-risk patients are offered therapies that range from observation (in patients who are asymptomatic with relatively well-preserved blood counts), to growth factors

such as erythropoietin (in patients with anemia), to immunosuppressive therapy (in patients with multiple cytopenias). Therefore, elements that factor into risk stratification are of critical therapeutic importance. Contemporary approaches to risk refinement, including the use of more discriminant prognostic models, such as the IPSS-R, are highly encouraged. Data are evolving to support the potential utility and applicability of models that combine comprehensive targeted molecular profiling with clinical models, such as the IPSS-R, in making treatment decisions, and they deserve prospective validation.

Supportive Care/Growth Factor Therapy

Lower-risk patients with anemia may benefit from erythropoietin (EPO) therapy. Predictors of response include lower serum EPO level (< 500 U/L) and a lower transfusion requirement (< 2 units of red cells per month). Response rates in such patients may be as high as 60%; however, it is substantially lower (less than 10%), in the absence of the above criteria.[32] Since most responses to EPO will occur within 8 weeks, a time limited trial of 8 weeks is reasonable when EPO is being used for treatment of MDS.

Immunosuppressive Therapy

Immunosuppressive therapy (IST) with antithymocyte globulin (ATG)-based therapies[33] are reasonable to consider in lower-risk patients with MDS who have multiple cytopenias, who are younger (< age 55), and who are positive for the HLA DR15 allele. These latter factors were positive predictors of response to IST.[34] A hypocellular marrow, which suggests a disease more closely aligned with aplastic anemia, also has been found in some studies to be predictive of response, but it has not been confirmed in others.[35,36] Since activated T cells are the target of IST, a predictive model that consists of a T-cell activating signature and duration of disease also has been proposed.[37]

Lenalidomide

In patients with deletion 5q (del[5q]) and lower-risk disease who require red cell transfusions, the use of lenalidomide is associated with a transfusion independence rate in the 70% range, with a median duration of response of 2.2 years.[38] In lower-risk patients with MDS without the del(5q), the response rate is in the 25% range and response duration is substantially shorter.[39] High karyotypic complexity, lower platelet count, and TP53 mutations tend to be associated with lenalidomide resistance, even in the presence of del(5q).[40] Lenalidomide currently is being investigated in combination with erythropoietin in a phase III trial in lower-risk patients with MDS. In this trial, it is hypothesized that the combination of lenalidomide and EPO will potentiate erythroid response in patients who have failed to respond to EPO or in whom EPO is predicted to have a low probability of being effective. The trial is based at least in part on promising results from an early phase trial that investigated the combination.[41] Recently, a novel mechanism of action involving lenalidomide-induced degradation via cereblon— of casein

kinase 1, alpha-1 (CSNK1A1), located on 5q32, and which results in further reduction of haploinsufficient expression of CSNK1A1—has been implicated in the sensitivity of del(5q) MDS to lenalidomide.[42]

Hypomethylating Agents

The U.S. Food and Drug Administration (FDA) has approved hypomethylating agents (HMAs) 5-azacytidine (azacitidine) and 5-aza-2′deoxycitidine (decitabine) for treatment of patients with MDS. These compounds become incorporated into DNA—although azacitidine also gets incorporated into RNA—and form a covalent complex with the DNA methyltransferase (DNMT) enzyme, which results in trapping and degradation of the enzyme and progressive loss of DNMT activity within the cells and subsequent DNA hypomethylation. When administered at very high doses, the cytotoxic effects of the agents predominate. However, lower doses in the range used for treating patients with MDS are postulated to allow the hypomethylating effect and, thus, epigenetic modulation to occur.[43]

Both agents have been investigated in randomized trials of patients with MDS. They are associated with similar objective response rates of complete response and partial response in the 15% range, although an additional 15% to 30% of patients will experience hematologic improvement, manifested primarily as an improvement in cytopenias and transfusion requirements.[44-46] Improvements in quality of life also have been demonstrated.

In addition, azacitidine has been associated with an overall survival advantage in patients with higher-risk MDS, when compared to prespecified conventional care regimens (including supportive care, low-dose cytarabine, and acute myeloid leukemia (AML) type–induction therapy), with median survival of 24.5 months in the azacitidine arm compared with 15 months in the control arm.[44] A population-based study also confirmed this 24-month survival benefit with azacitidine use outside of a clinical trial setting.[47]

Although the benefit associated with the use of HMAs in patients with MDS is indisputable, many patients will not benefit from them. Furthermore, for those who respond, the response is not immediate. The median time to best response is in the range of 3 to 4 months. Therefore, biomarkers that predict response to therapy would be of substantial value. Our increasing knowledge of the molecular genetic landscape of MDS—including the fact that mutations affecting enzymes that are involved in DNA methylation are involved in MDS pathogenesis— has spurred additional efforts in recent years to find predictive biomarkers to HMA therapy. As such, TET2 mutations or DNMT3A mutations were associated with a modest increase in response rates to HMA therapy in earlier reports with conventional Sanger sequencing.[48,49] A more recent report used a more comprehensive molecular profiling approach. It evaluated 40 recurrently mutated genes in 213 patients with MDS treated with HMAs and confirmed clonal TET2 mutations as predictive of response (odds ratio, 1.99).[50] In contrast, TP53 and PTPN11 mutations were associated with shorter overall survival after

HMA treatment, but they did not predict response. These findings require validation in prospective clinical trials. Presently, insufficient evidence exists to suggest that the decision to treat patients with HMAs can be made on the basis of mutational profiling alone, especially since responses to HMAs were observed even in patients with mutations that confer a very poor prognosis.[50]

Combination Therapies

There remains an urgent need for the development of new drug therapies and combinations to treat patients with MDS. An early focus was the combination of HMAs with histone deacetylase inhibitors (HDACi).[51-55] This was based on the hypothesis that inhibiting two pathways of epigenetic deregulation would be potentially synergistic, and abundant preclinical evidence of synergy. Early phase trials investigating the combination of azacitidine with the HDACi entinostat or vorinostat,[52,56] or the immunomodulatory agent lenalidomide,[57] yielded promising results, which has led to randomized trials conducted in the intergroup setting.

The results of randomized trials conducted in the U.S. intergroup setting (E1905) comparing azacitidine versus azacitidine plus entinostat,[58] and preliminary results of the recently concluded three-arm randomized phase II North American intergroup trial (S1117) comparing single-agent azacitidine to azacitidine plus vorinostat and azacitidine plus lenalidomide combinations,[59] respectively, however, have shown no significant advantage to the combination arms as to improvement in response rates. Therefore, azacitidine remains the standard of care. Survival endpoints, either progression-free or overall survival, may be more relevant primary endpoints of future large randomized efforts that compare single-agent HMA therapy to novel combinations and approaches.

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Individual decision making on whether to consider alloSCT as a possible treatment option in treating patients with MDS requires the accurate assembling of several disease- and patient-characteristics.

Disease Characteristics

In general, MDS includes an extremely heterogeneous group of myeloid malignancies with different natural courses and life expectations. Therefore, a risk-based approach for individual decision making on treatment strategy is highly suggested, and it is mandatory when referring patients for alloSCT.[8,10,60] Together with the nosological classification methods (such as the FAB and, more recently, the WHO classification schemes), prognostic scoring systems in MDS have been considered the most appropriate tools for treatment stratification. For almost 15 years, the IPSS[15] has been universally recognized as the landmark reference method for risk-stratification with patients classified in high-risk catego-

ries (including intermediate-2 and high-risk groups) as generally being considered for early alloSCT. However, a different treatment plan usually is recommended for patients in the lower IPSS risk categories (i.e., low and intermediate-1). In a foremost decision-analysis study that included patients younger than age 60, delayed transplantation was shown to associate with maximal life expectancy, with an even more marked survival advantage for patients under age 40.[61] In 2007, a time-dependent WHO classification-based prognostic scoring (WPSS) incorporating transfusion dependence was proposed for untreated patients.[16] Different from IPSS, the WPSS identifies five risk groups of patients with different survival, and it allows for real-time assessment of prognosis in MDS. Its relevance after alloSCT was validated in a subsequent study from the GITMO group that included 406 patients,[62] in which a multivariate Cox survival analysis also included age and sex of patient, time between diagnosis and alloSCT, year of transplantation, disease stage at transplantation, source of stem cells, type of donor, and type of conditioning, WPSS showed a prognostic significance on both overall survival and probability of relapse. The validity of WPSS in predicting outcomes after alloSCT in patients with MDS recently was confirmed in a population of 60 Southeast Asian patients.[63]

Cytogenetics appears to be the most critical factor in determining survival in patients with MDS. However, the cytogenetic categories included in all of the proposed prognostic scoring systems were derived from large series of patients who were only treated with supportive care. Because alloSCT represents a treatment strategy that is potentially capable of eradicating the hematopoietic malignant cell clone, it could be postulated that the prognostic significance of cytogenetics would persist using this treatment approach. However, the negative effect of poor-risk cytogenetics on the outcomes of patients with MDS undergoing alloSCT has been confirmed.[64-69] For example, a recent retrospective analysis from the European Society for Blood and Marrow Transplantation (EBMT) demonstrated that poor-risk cytogenetics, as defined by standard IPSS scores, were associated with a relatively poor survival after alloSCT from HLA-identical siblings, except in patients with low marrow blast count (i.e., RA/RARS) who were transplanted up front.[69]

In 2012, the revised IPSS (IPSS-R) for MDS was generated by analyzing 7,012 patients in a new international collaborative effort. Based on a new comprehensive cytogenetic score,[20] and considering severity of cytopenias by incorporating different cutoff points, the IPSS-R stratifies five risk groups with different clinical outcomes.[19]

The ability of the new cytogenetic risk classification to predict post-transplant outcome was promptly confirmed in a series of 1,007 patients who underwent alloSCT at the Fred Hutchinson Cancer Research Center in Seattle. A substantially higher rate of relapse and mortality rate was found in patients with very poor cytogenetics compared to patients with good-risk cytogenetics.[70]

An additional disease characteristic recently has been shown to negatively affect the prognosis of patients with

MDS. Not included in any of the previously described scoring systems is the presence of a monosomal karyotype (MK) (i.e., the presence of two or more distinct autosomal monosomies or a single monosomy associated with a structural abnormality).[71-74] However, an association of MK with lower survival, higher relapse incidence, and overall mortality after alloSCT— even among patients with a complex karyotype— has been reported consistently.[70,75-77]

The effect of the IPSS-R on alloSCT outcomes recently was demonstrated in an analysis from the Italian GITMO cooperative group that included 374 patients with primary MDS. Both IPSS-R and monosomal karyotypes were independently associated to a lower overall survival and a higher relapse probability by multivariate analysis.[78] In this study, a predictive model of post-transplant outcome in patients with MDS (Transplantation Risk Index) was originated based on the age of the patient, IPSS-R category, monosomal karyotype, hematopoietic cell transplantation (HCT)-specific comorbidity index, and refractoriness to induction chemotherapy.

In addition to cytogenetics, other disease characteristics have been associated with a poor prognosis in patients with MDS. These include severe bone marrow fibrosis,[79,80] refractory life-threatening cytopenias,[81-83] and gene mutations.[2,18,24,25,28,29,84-89]

As to the effect on alloSCT outcome, bone marrow fibrosis, a recent EBMT retrospective analysis of 721 patients with MDS demonstrated that only severe fibrosis was shown to affect survival, whereas patients with mild or moderate fibrosis had an alloSCT outcome comparable to patients without bone marrow fibrosis.[79] For gene mutations, an independent association with a shorter post-transplant overall survival, after adjusting for clinical variables and complex karyotype status, recently has been reported for mutations in *TP53* and *TET2*.[90]

Patient Characteristics

Apart from disease characteristics, host-specific risk assessment in determining indications for alloSCT always should be grounded on essential patient-related factors, including age, comorbidities, and donor availability.

Although usually considered as a treatment option for patients younger than age 60, over the last 2 decades the development of reduced-intensity conditioning (RIC) regimens, together with substantial progress in supportive care measures, have resulted in an increase in the upper age limit to age 70 (occasionally even older) in carefully selected very-fit patients. Because MDS are much more common in older people (median age at diagnosis, over age 70), with only 10% of patients younger than age 50, this age-limit extension translates to a considerable expansion in the proportion of patients for whom an alloSCT treatment strategy might be presently contemplated.[91,92] Indeed, an international collaborative retrospective comparison of two well-balanced cohorts of medically fit patients with high-risk MDS defined by age 60 to 70 and ECOG PS of 2 or less, treated with alloSCT (103 patients) in case of donor availability, or 5-azacytidine (75 patients) in case of no donor availability, suggested a survival advantage in favor of allogeneic transplantation.[93] Ad-

ditionally, recently reported results of an international collaborative decision analysis (evaluating both life expectancy and quality-adjusted life expectancy) indicated a significant benefit (p < 0.001) of RIC alloSCT versus nontransplantation therapies in patients' age 60 to 70 with intermediate-2/high-risk IPSS de novo MDS.[94]

However, a sophisticated statistical analysis of a large population of older patients with advanced MDS compared alloSCT (247 patients, reported to the EBMT) with nontransplant approaches (137 patients, reported to the Düsseldorf registry). The analysis indicated a possible nonsignificant survival disadvantage for the transplant cohort because of the higher nonrelapse mortality.[95] These results suggest that a prospective controlled randomized study that addresses the "intention to go for transplant" question is absolutely necessary.[95]

Comorbidities have been shown to crucially affect alloSCT clinical outcomes in several hematological malignancies. These data led to the development of a hematopoietic cell transplantation-specific comorbidity index (HCT-CI) as a useful tool for risk assessment before transplantation.[96] The risk-stratification ability of the HCT-CI in patients transplanted for AML and MDS subsequently was confirmed both in the reduced-intensity and myeloablative conditioning strategies.[97-100] The HCT-CI also was prospectively validated by the GITMO group in a consecutive cohort of 1,937 patients receiving alloSCT in Italy over 2 years, including 199 patients with MDS. In 2011, a time-dependent MDS-specific Comorbidity Index (MDS-CI) was developed on a learning cohort that included 840 patients diagnosed in Pavia, Italy. It was subsequently validated in an independent cohort of 504 patients diagnosed in Düsseldorf, Germany.[101] Since it has been shown to provide additional prognostic information on patients stratified according to the IPSS-R, the MDS-CI may represent a valuable tool in support of the HCT-CI when evaluating patients for possible transplant indication.

High-serum ferritin and iron overload secondary to pretransplantation transfusion also is associated with a substantial negative effect on nonrelapse mortality after alloSCT.[102-110] Thus, transfusion history in patients with MDS should be considered for transplantation decision-making as well as for initiation of a timely iron chelation therapy to prevent iron accumulation before transplant.

When to Transplant

Although very heterogeneous, the natural course of MDS typically is characterized by a disease progression with patients exhibiting gradual worsening of peripheral blood cytopenias, which eventually lead to transfusion dependency. Sequential marrow examination, especially in the presence of myeloblast excess (i.e., ≥ 5%), often can demonstrate an increase in marrow blast– count culminating in AML evolution. Cytogenetics tend to remain stable, even though the occurrence of chromosome aberrancies (or additional ones, when already present at diagnosis) occasionally may be observed. Time-dependent disease modifications are outlined

as phase progression by the WPSS and the IPSS/IPSS-R classification system, IPSS-R.[15,16,19]

The Markov retrospective analyses cited above have shown a substantial survival advantage for patients who are in high-risk categories of MDS (intermediate-2 and high-risk, according to IPSS) undergoing early alloSCT from HLA-matched donor, whereas a transplant deferment until disease progression seems to confer longer life expectancies in patients with lower-risk MDS (low- and intermediate-1 risk, according to IPSS).[61,94] In general, because the status of the disease at transplant has a major effect on all outcomes, better long-term results seem to be achieved when transplantation is performed earlier during the course of the disease.[62,111,112] In addition to disease progression, risk associated with transplant delay may include occurrence of infectious complications, acquisition of transfusion refractoriness, iron overload secondary to transfusion history, performance status decline, and acquisition of additional comorbidities, which lead to a substantially higher risk of nonrelapse mortality following transplantation. Nonetheless, the question of the optimal time for alloSCT in individual patients may be difficult, because of the unavoidable morbidity and nonrelapse mortality risks associated with the transplantation procedure and to the current availability of alternative treatment options, such as HMAs. In a recent GITMO decision study that included 660 patients with MDS who received best supportive care and 449 who underwent transplantation, a continuous-time multistate Markov model was applied to describe the natural history of the disease and to evaluate the effect of alloSCT on survival.[113] Results of this study indicate that a delayed transplantation is advisable only for patients with early disease (low-risk by IPSS, very low- and low-risk by WPSS), with the best survival benefit deriving from alloSCT for patients classified in the intermediate-1, according to IPSS (in the presence of multilineage dysplasia and/or transfusion dependency) or the intermediate WPSS risk category.

Furthermore, new and interesting information that could be combined for clinical decision making in patients with MDS may originate from a further retrospective GITMO study. This study was recently performed in a large population of 529 patients with MDS without a compatible family donor but with plain indication for alloSCT. A competing risk analysis unveiled high pretransplant risk of disease evolution and mortality resulting from the time spent waiting for the identification of a suitable unrelated donor, both on the entire population of patients with MDS and on specific subgroups stratified by disease risk and age (GITMO Registry, M. Della Porta, personal communication, 2015). If confirmed in other series, these findings would support selection of haploidentical donors to perform immediate alloSCT in patients with high-risk MDS without a promptly available HLA-matched donor.[114,115]

Apart from obviously depending on donor availability, the decision on when to transplant in MDS often has to consider potential treatment to be administered before transplantation, especially in patients with a higher percentage of marrow to possibly downstage the disease to a lower-risk category.[116-118] Because AML-like induction chemotherapy, besides being rather toxic in older patients, is frequently leading to disappointing results in MDS, especially in the presence of high-risk cytogenetics, HMAs frequently are preferred in the interim period before transplantation. Life expectancy has been shown to be very dismal for patients with loss of response to azacitidine.[119,120] In patients whose disease responds, alloSCT possibly should be offered before disease progression, if a donor is available. Presently, because of the absence of randomized studies, optimal pre-transplantation therapy is unknown,[121] although trials with HMAs employed as a bridge to transplant are currently ongoing.

In conclusion, individual decision making on the best treatment strategy pertaining to allogeneic transplantation is usually the consequence of a difficult composite judgment that includes disease-, patient-, and transplant-characteristics together with the patient's expectations and opinions.

GENETICS IN MYELODYSPLASTIC SYNDROMES/MYELOPROLIFERATIVE NEOPLASMS

MDS/MPNs represent an optimal disease model for the clinical implementation of broad spectrum mutational profiling. First, the clinical and pathologic characteristics of MDS/MPNs are challenging to recognize, and they often can change within the context of cytoreductive agents or other therapies. Second, the spectrum of mutations in MDS/MPNs is relatively well-characterized and allow for the sensitive annotation of clonality in most patients. Lastly, although substantial overlap occurs among recurrent mutations in MDS/MPNs, it could be argued that each disease entity is characterized by a unique genetic fingerprint that may aid in diagnosis. Emerging evidence suggests that these genetic lesions are independently prognostic and may aid in therapeutic decisions. Below is a disease-specific summary of recurrent mutations and their clinical relevance (Table 2).

Chronic Myelomonocytic Leukemia

The hematologic phenotype of chronic myelomonocytic leukemia (CMML) is defined by a peripheral monocytosis and dysplasia.[122] The recurrent genetic mutations associated with this CMML phenotype converge on diverse pathways that include mutations of signal transduction (*NRAS, KRAS, CBL, JAK2*); DNA methylation (*DNMT3A, TET2, IDH 1/2*); transcriptional regulation (*ETV6, RUNX1*); chromatin modification (*EZH2, ASXL1*); and the RNA splicing machinery (*SF3B1, SRSF2, ZRSR2, U2AF1*).[123-125] Although the pathways affected are heterogeneous, a genetic clonal event can be identified in greater than 90% of CMML cases by sequencing only nine genes. In fact, mutations in *TET2, ASXL1*, and *SRSF2* are highly recurrent with each identified in up to 45% of patients.[125-127] This allows for the CMML clinician to obtain evidence of clonality in almost all cases of suspected CMML, making it straightforward to parse malignant from reactive monocytosis. Additionally, co-mutation of *SRSF2*

TABLE 2. Frequency of Recurrent Mutations among WHO-defined MDS/MPNs[4,136,139,144]

Mutation	CMML	JMML	aCML	MDS/MPN-U	RARS-T	Clinical Significance
ASXL1	40	0	69	Unknown	15	Adverse
CALR	0	0	0	0	<1	Unknown
CBL	10*	15**	0	Unknown	4	Adverse/Favorable
CSF3R	0	0	Variable	0	0	Predictive
DNMT3A	2	0	Unknown	Unknown	15	Unknown
ETV6	<1	0	Unknown	Unknown	3	Unknown
EZH2	5	0	Unknown	10	Unknown	Unknown
IDH1/2	6	0	Unknown	Unknown	Unknown	Unknown
JAK2	8	0	7	19	57*	Favorable
JAK3	Unknown	12	Unknown	Unknown	Unknown	Neutral
K/N RAS	19	39	35	14	Unknown	Neutral
NF1		13	Unknown	Unknown	Unknown	Neutral
PTPN11		44	Unknown	Unknown	Unknown	Neutral
RUNX1	15	0	Unknown	14	Unknown	Neutral
SETBP1	15*	8	48	10	1	Adverse
SF3B1	6	0	Unknown	Unknown	93	Favorable
SRSF2	46	0	Unknown	Unknown	7	Adverse
TET2	58	0	Unknown	30	25	Neutral
TP53	<1	0	Unknown	Unknown	Unknown	Unknown
U2AF1	5	0	Unknown	Unknown	5	Unknown
ZRSF2	8	0	Unknown	Unknown	3	Unknown

Abbreviations: WHO, World Health Organization; MDS/MPNs, myelodysplastic syndromes/myeloproliferative neoplasms; CMML, chronic myelomonocytic leukemia; JMML, juvenile myelomonocytic leukemia; aCML, atypical chronic myeloid leukemia; MDS/MPN-U, myelodysplastic syndromes/myeloproliferative neoplasms-unclassifiable; RARS-T, refractory anemia with ring sideroblast and thrombocytosis.

and *TET2* is highly specific for patients with CMML, which aids in the diagnosis of the treated CMML patient when historic monocytosis may be unclear and current monocytosis may be suppressed by HMAs or cytoreductive agents.[31]

The prognostic significance of recurrent mutations in CMML also has been tested. Interrogation of the most common mutations in CMML has identified *ASXL1* to be independently prognostic.[48,73] This has led to its incorporation into two independent prognostic scoring systems. However, larger data sets will be required to fully annotate the prognostic significance of single and combination mutations in CMML.

Juvenile Myelomonocytic Leukemia

Although the monocytic phenotype of juvenile myelomonocytic leukemia (JMML) is similar to that of CMML, the genetic fingerprint of JMML is distinct.[128] Greater than 90% of recurrently mutated genes in JMML cluster on RAS pathway activation.[129] These gene mutations include *NF1, N-RAS, K-RAS, PTPN-11,* and *CBL*.[130,131] Both somatic and germline mutations of these genes have been identified, with the latter most associated with congenital genetic syndromes such as Noonan syndrome (PTPN11) and Neurofibromatosis type 1 (NF1).[132-134] Secondary events in *JAK3* and *SETBP1* also have been described and suggest a poor prognosis.[135,136] This genetic landscape, along with its characteristic GM-CSF

hypersensitivity, has resulted in major advances in the molecular understanding of JMML.[128] Further, the presence of these mutations can alter treatment decisions and management. Patients with *CBL* mutations and its associated congenital syndrome can manifest a JMML phenotype that is self-limited.[131] Therefore, a watchful waiting strategy is often employed in these children, as opposed to allogeneic transplant in other RAS-mutated JMML cases.[137]

Atypical Chronic Myeloid Leukemia

Atypical chronic myeloid leukemia (aCML)Atypi is a disease characterized by severe neutrophil dysplasia and cytopenias in the absence of the BCR:ABL fusion protein. This disease has historically been difficult to diagnose given the pathologic overlap between it and other MDS/MPNs, particularly MDS/MPN-Unclassifiable. Further, the diagnostic difficulty present in discerning aCML from chronic neutrophil leukemia (CNL) has made the annotation of aCML-specific mutations challenging.[138] Gene mutations identified in aCML/CNL include *JAK2, SETBP1, NRAS,* and *CSF3R*. Analysis of these genes can identify a clonal event in over 50% of these diseases.[139-141] *CSF3R* mutations are notable because they represent a potential predictive marker for targeted therapy. Preclinical data suggest that truncating CSF3R mutations predict sensitivity to SRC inhibition and *CSF3R* mutations affecting the membrane proximal portion for the receptor

predicts sensitivity to JAK2 inhibition.[139] The latter has been validated in clinical case reports with ruxolitinib therapy in aCML.[142] However, two separate reports have failed to identify CSF3R mutations in a stringently defined aCML cohort and were exclusively seen in CNL.[143,144] Nonetheless, mutational analysis for *CSF3R* should be performed if aCML is suspected, given the potential therapeutic implications.

Myelodysplastic Syndromes/Myeloproliferative Neoplasms–Unclassifiable

The genetic study of MDS/MPN-Unclassifiable (U) has been limited by difficulties in the diagnostic standardization of this entity. MDS/MPN-U is defined by having clinicopathologic features of myeloproliferation, dysplasia, and cytopenias but not meeting criteria for other well-defined MDS/MPNs. It is hypothesized that many MDS/MPN-U cases may be reclassified into other WHO-defined MDS/MPNs with mutational profiling. To this end, a recent retrospective study identified a clinical and genetic signature that could identify aCML among those cases initially identified as MDS/MPN-U.[144] More investigation is needed to better annotate disease-specific genetic fingerprints to confidently allow for reclassification of MDS/MPN cases.

Refractory Anemia with Ring Sideroblast and Thrombocytosis

Refractory anemia with ring sideroblast and thrombocytosis RARS-T) is defined by the presence of ringed sideroblasts and a platelet count of greater than 450×10^8/dL and is included as a provisional category within the group of MDS/MPN-U by WHO.[8,14] Similar to cases of MDS with ringed sideroblasts (RARS), the genetic landscape of RARS-T is dominated by the presence of mutations in *SF3B1* that occur at a frequency reported between approximately 60 to 90%.[28,29,145] Other recurrent mutations identified in both RARS and RARS-T include *TET2*, *ASXL1*, and *EZH2*.[146] However, RARS-T has been demonstrated to additionally harbor mutations in *JAK2* at rates approximating 50% and, less frequently, mutations in other signaling mutations such as *CBL* and *CALR,* which are rarely seen in RARS.[28,146-149] This raises the possibility that mutations in *JAK2* may be responsible for the thrombocytosis uniquely seen in RARS-T.

Although conventional wisdom states that the natural history of RARS-T is relatively benign, emerging data suggest that annotation of mutations in RARS-T may reveal a more aggressive subtype. A recent report identified *SF3B1* and *JAK2* mutations as favorably prognostic and associated with improved survival compared to their mutated counterpart. For example, *SF3B1* wild-type cases of RARS-T had a median survival of 3.3 years compared to 6.9 years in mutated cases.

THERAPIES IN ADULT MYELODYSPLASTIC SYNDROMES/MYELOPROLIFERATIVE NEOPLASMS

No pharmacologic agents have been demonstrated to alter the natural history of MDS/MPNs. As such, the general ap-

proach for the treatment of these groups of diseases is to focus on therapeutic strategies tailored to symptomatology with individual patients. There is little evidence to suggest that patients with asymptomatic MDS/MPN benefit from current standard treatment. However, it is strongly recommended that all patients with MDS/MPN be considered for clinical trial when available. Allogeneic stem cell transplant has the most robust data suggesting a disease modifying effect in MDS/MPNs[94,150-152] and should therefore be considered in higher-risk patients with MDS/MPN. Although there has been substantial progress in the prognostication of CMML cases, challenges remain in adequately risk-stratifying other MDS/MPNs for clinical transplant decision making.[48,153,154] Below is a summary of treatment options and their disease-specific supporting data.

Hypomethylating Agents

Very limited data are available for the use of HMAs for the treatment of aCML, MDS/MPN-U, or RARS-T.[155] However, robust data exist that demonstrate the activity of HMAs in CMML. Several phase II studies have demonstrated that azacitidine is active in CMML and associated with acceptable therapy-associated toxicity.[156,157] Oral azacitidine more recently has been tested for the treatment of CMML with clinical responses seen in 35% of patients previously treated with HMA for MDS and CMML, and in 73% of patients receiving azacitidine as first-line therapy.[158] Decitabine also has been examined in multiple phase II trials, with response rates ranging from 10 to 58% in patients with CMML.[159] However, despite well-documented activity, no evidence exists that HMAs increase overall survival or decrease progression to AML. Therefore, we reserve this therapy for patients with CMML in which cytopenias are the predominant symptom. We would not favor HMAs in rapidly proliferative patients with CMML, given the relatively long median time to HMA response. There is no CMML-specific evidence to favor one HMA over another.

Lenalidomide and Interferon

There has been limited data testing the activity of lenalidomide in CMML and RARS-T. In CMML, lenalidomide has been tested in combination with metronomic doses of melphalan. Although the study was small in number, a 25 and 33% response rate was identified in patients with myelodysplastic and myeloproliferative CMML, respectively.[160] A case study also has reported a proliferative of CMML cases with isolated del(5q) treated with lenalidomide that achieved blast clearance and cytoreduction. In RARS-T, three case reports have demonstrated clinical activity with respect to hematologic and splenomegaly improvement irrespective of cytogenetic abnormalities.[161-163] Interferon has been tested in aCML in a limited number of cases with modest activity.[164,165]

Cytoreductive Agents

Patients with MDS/MPN with rapid and severe myeloproliferative or constitutional symptoms should be considered for treatment with cytoreductive agents. These therapies range

from induction chemotherapy to hydroxyurea and should be chosen based on performance status and other host-specific factors. As with HMAs, a larger clinical experience exists with cytoreductive agent in CMML compared to other MDS/MPNs. Several studies have reported the efficacy of the topo-isomerase inhibitors topotecan and etoposide both as single agent and in combination with cytarabine.[166-168] Other trials have examined combination with arsenic or all-trans retinoic acid (ATRA) with modest results.[169,170] These two trials are notable because they represent two of the only MDS/MPN-specific studies to date. The only randomized study that has been performed in CMML randomly assigned 105 patients with CMML to receive hydroxyurea or etoposide. Surprisingly, this trial demonstrated a median overall survival of 20 months in the hydroxyurea group compared to 9 months in the etoposide arm, suggesting inferior disease-modifying capacity for etoposide in CMML.[168] Induction chemotherapy has been used in CMML based on extrapolation from MDS. In our practice, we recommend induction chemotherapy in patients with extreme or symptomatic leukocytosis, massive splenomegaly, or severe constitutional symptoms that are refractory to hydroxyurea or other less-intensive approaches. Although it is not well addressed in the literature, a minority of patients achieves a complete response and are capable of being considered for allogeneic stem cell transplant. However, limited evidence is available that carefully weighs these response rates against the substantial toxicities associated with induction-type chemotherapy.

Future Therapies

Although other therapeutic options have the potential to improve the symptomatology of patients with MDS/MPN, the current pharmacologic landscape is limited. Ongoing studies testing JAK2 inhibitors in aCML and CMML hold promise[171] (NCT02092324 and NCT01776723). However, only a small number of studies currently are addressing MDS/MPN cases specifically. Hopefully, improved molecular understanding of MDS/MPNs will lead to disease-specific clinical trials with promising agents that will affect the natural history of this group of lethal diseases.

CONCLUSION

Our burgeoning knowledge of the molecular complexity of MDS and MDS/MPNs is rapidly providing novel insights into the pathobiology of these diseases. The clinical application and relevance of these insights currently is largely limited to the refinement of prognostic risk models. Hopefully, this knowledge ultimately will translate into targeted therapies with the potential to change the natural history of these diseases. Presently, judicial selection of patients for treatment with currently available therapies, including alloSCT and nontransplant disease-modifying therapies, coupled with an improved knowledge into the best approaches to use these therapies, is of paramount importance. Given the current paucity of effective therapies for these diseases, an urgent need remains for the development of novel approaches and combinations with the potential of moving the field forward.

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LUNG CANCER

Beyond Second-Line Treatment in Non–Small Cell Lung Cancer and Small Cell Lung Cancer: What to Do When the Data End?

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Beyond "Second-Line" in Non–Small Cell Lung Cancer: Therapy and Supportive Care

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OVERVIEW

Although there once was a single algorithm for the treatment of patients with advanced lung cancer, the modern treatment of advanced lung cancer has multiple treatment pathways that depend on multiple factors, including histology and molecular subtype of disease. New molecular targets, targeted agents, and modes of therapy for patients, including immunotherapy, are being identified at an accelerating pace. These advances are changing outcomes and the treatment landscape, but they also highlight situations with inadequate data to support the use of cytotoxic chemotherapy. In this article, we provide an overview of data regarding cytotoxic chemotherapy and targeted therapy and their value after second line, review the critical role of supportive care and palliative care, and emphasize the importance of advance care planning with our patients. Although this article focuses primarily on NSCLC, the comments about palliative care and advanced care planning also apply to patients with small cell lung cancer.

Although there once was a single algorithm for the treatment of patients with advanced lung cancer, the modern treatment of advanced non–small cell lung cancer (NSCLC) has multiple treatment pathways that depend on many factors including histology and molecular subtype of disease. In addition, new molecular targets, targeted agents, and modes of therapy, including immunotherapy, are being identified at an accelerating pace. These advances are changing outcomes and the treatment landscape, but the rapid introduction of many new therapies may be somewhat bewildering for the practicing oncologist. In this context, a discussion of therapy's role beyond second line is outdated. However, more relevant than ever is the medical oncologist's role in advocating for patients to have access to these advances, discerning the patient's care goals, and sparing them from the toxicities of unproven therapies.[1] This article will review critical factors for decision making in this changing treatment environment.

THE ROLE OF CHEMOTHERAPY IN THIRD-LINE AND BEYOND

Unlike the data establishing the role of docetaxel in the second-line treatment of advanced NSCLC,[2] there are no randomized trials evaluating chemotherapy in the third- and fourth-line treatment of advanced NSCLC. There are multiple single-institution and retrospective analyses (selected data is presented in Table 1). The results of chemotherapy in the third and fourth line are strikingly variable across these studies. This may reflect different patient characteristics or underlying tumor biology. Results from Asia—which are generally more favorable than those from the West—are consistent with previous observations that Asians have a better prognosis. There clearly is some heterogeneity in progressive lung cancer, and some patients will respond better than others to further treatment. There is a suggestion that response to previous treatment and continued good performance status are predictors of benefit from third- and fourth-line chemotherapy, but these conclusions must be viewed with caution given the absence of randomized data.

TARGETED THERAPIES FOR PATIENTS WITH A TARGET

Today broad molecular profiling is the standard of care for patients with lung adenocarcinomas,[3] and the identification of actionable molecular targets in squamous NSCLC is an area of active investigation.[4] Furthermore, the number of effective therapies has expanded. As an example, for patients with ALK-positive lung cancers, four lines of therapy have shown meaningful clinical benefit (two "targeted" and two "conventional"). Survival for some molecular subtypes of NSCLC is now measured in years rather than weeks.

Although evidence supporting the use of third- and fourth-line standard cytotoxic chemotherapy is largely retrospective and of poor quality, prospective data support the use of targeted therapies in patients with defined molecular targets, even when patients have had multiple prior lines of therapy.

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TABLE 1. Selected Retrospective Series Describing Outcomes to Third- and Fourth-Line Chemotherapy in NSCLC

Author	Patients	ORR	mOS
	Third Line/ Fourth Line	Third Line/ Fourth Line	Third Line/ Fourth Line
Massarelli[22]	43/14	2%/0%	5 mo/6 mo
Asahina[23]	230/106	17%/11%	12 mo/10 mo
Younes[24]	214/NA	7%/NA	8 mo/n/a
Chen[25]	123		13 mo/13 mo

Abbreviations: NSCLC, non-small cell lung cancer; ORR, overall response rate; mOS, median overall survival; mo, months; NA, not available.

In 2011, crizotinib was approved for treatment of patients with metastatic ALK-positive lung cancer. In the phase I trial that led to the accelerated approval of crizotinib, more than 53% of patients had two or more lines of prior therapy.[5] In all treated patients, the overall response rate was 61% and the median progression-free survival was 10 months. Importantly, in patients with two prior therapies, the response rate was 65%, and in those with three or more prior therapies, the response rate was 59%, emphasizing that when ALK rearrangements are present, use of this targeted ALK inhibitor is beneficial to the patient. Consonant with this notion, the U.S. Food and Drug Administration's approval of crizotinib for ALK-positive lung cancer does not refer to a line of therapy (unlike the label for all cytotoxic chemotherapies). Similarly, after the identification of ROS1 as a target for crizotinib, a group of patients was prospectively identified and treated with crizotinib.[6] Forty-four percent of patients in this study had two or more prior lines of therapy. The overall response rate of patients in this study was 72%, and the median progression-free survival was 19 months.

Although the use of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in first-line treatment of patients with EGFR-mutant NSCLC has clear benefit, patients typically develop clinically acquired resistance to erlotinib, gefitinib, or afatinib within 1 year. As a mechanism of resistance, many patients develop a secondary mutation, EGFR T790M, that alters the binding of tyrosine kinase inhibitors, allowing continued

KEY POINTS

- Although there are no randomized studies, data suggest patients with good performance status and previous response to chemotherapy are more likely to benefit from further chemotherapy.
- Targeted therapy can have significant benefit in previously treated patients, particularly when new targets are identified.
- All patients with advanced lung cancer should receive palliative care.
- Advanced care planning and conveyance of realistic expectations about outcomes should be discussed with all patients.

growth of the cancer.[7] More recently, drugs, including AZD9291 and rocelitinib, have been developed that target EGFR T790M. In studies exploring the efficacy of these agents, the enrolled patients have had multiple prior lines of therapy. For both AZD9291 and rocelitinib, the median number of prior therapies for patients treated was three, with some patients having as many as 12 prior lines of therapy.[8,9] For AZD9291 in 205 evaluable patients, the response rate was 53%. For rocelitinib, among the 40 patients with EGFR T790M–positive evaluable disease treated in the therapeutic dose range, the response rate was 58%.

Taken together, these data with crizotinib, AZD9291, and rocelitinib suggest that, in patients who have the target of interest, multiple prior lines of therapy did not affect the patient's likelihood of benefit. Therefore, for patients with NSCLC, it is imperative that we identify all targetable driver oncogene alterations. For those patients who had insufficient tissue for molecular testing at the time of diagnosis, in some clinical situations it is reasonable to consider repeat biopsy solely for molecular testing. In addition, new targets such as BRAF and MET have recently emerged, and other new targets continue to emerge. This may allow patients to enroll in clinical trials evaluating new targets and agents. Although it is hardly a sufficient predictor of likelihood of a targetable driver oncogene, never-smoking history is associated with the highest likelihood of presence of ROS1, ALK, or EGFR mutations. A recent analysis showed that a broad hybrid capture–based next generation sequencing (NGS) assay identified actionable genomic alterations in 65% of tumors from never or light smokers with lung cancers.[10] Notably, these results were from patients who had prior negative testing for actionable genomic alterations using non-NGS approaches. These findings support profiling of NSCLC tumors using NGS as a more comprehensive and efficient strategy than non-NGS testing.

THE IMPORTANCE OF PALLIATIVE CARE

The initial trials demonstrate a benefit of chemotherapy for patients with advanced NSCLC who were randomly assigned to best supportive care or best supportive care plus chemotherapy. However, the significance of supportive care, as well as some key elements of supportive care, were not appreciated until 2010 when Temel and collaborators published their single-institution, randomized trial demonstrating the benefit of early palliative care when integrated with standard oncologic care.[11] Patients with newly diagnosed metastatic NSCLC were randomly selected to receive a palliative care team (i.e., a board-certified palliative care physician and advanced-practice nurses) in addition to standard oncology care or standard oncology care alone. Palliative care visits occurred at least monthly. Patients assigned to early palliative care had a better quality of life as measured by the Functional Assessment of Cancer Therapy–Lung scale, experienced less depressive symptoms, and received less aggressive therapy at the end of life. In the control arm, 54% received aggressive end-of-life care compared with 33% on the palliative care arm (p = 0.05). Despite less aggressive therapy, patients who received early palliative therapy had a median sur-

vival of 11.6 months, compared with 8.9 months on the control group (p = 0.02).

It is unclear how this single-institution trial, with a specific group of physicians, translates to general practice. Whether these benefits of early palliative intervention can only be achieved by a specialized palliative care team is unknown, as is how easily the results could be achieved in the community oncology setting where access to such support services is often limited. Indeed, in 2010 only 59% of National Cancer Institute–designated comprehensive cancer centers and 22% of community cancer centers had outpatient palliative care programs.[12] A more recent survey of California hospitals with inpatient palliative care programs found that only one-fifth provided outpatient palliative services, and around the clock outpatient services were available in only one-quarter of those.[13] However, this work strongly suggests that more aggressive therapy at the end of life is not associated with a better survival.

Multiple studies have found that a significant number of patients with advanced NSCLC receive chemotherapy in the last month of life. A 2001 review of almost 8,000 Medicare patients found that 11% received chemotherapy in the last month of life.[14] An Italian review of four cancer centers found 33% of patients received chemotherapy in their last month of life (only one-third of these had lung cancer).[15] Fifteen percent of patients experienced grade 3 to 4 toxicity in the last month of life, and there were two treatment-related deaths. A clinical benefit was observed in 10%. A more recent retrospective chart review was conducted in 10 community oncology practices, which included 417 patients that were diagnosed with advanced NSCLC in 2000 to 2003.[16] Chemotherapy was given within 1 month of death in 43% and within 2 weeks of death in 20%. Of those receiving chemotherapy in the last month of life, 39% were first line, 28% second line, and 21% third line. The authors attributed this high use of treatment at the end of life to the availability of new agents and an increase in the length of time patients receive treatment.

ADVANCED CARE PLANNING

Emerging data suggest that interventions in community practice can affect end-of-life care. The US Oncology Network's My Care My Wishes program (MCMW) gives formal counseling to patients with advanced cancer, including discussions of prognosis and desires regarding code status and end of life. A recent analysis suggests that MCMW improves documentation of code status in electronic medical records in the community setting, perhaps reducing the likelihood of unwanted and futile end-of-life interventions.[17] A study at this meeting suggests that advanced care planning reduces hospitalization and increases hospice referrals in patients with advanced cancer.[18]

In 2014, the Institute of Medicine released "Dying in America: Improving Quality and Honoring Individual Preferences Near the End of Life."[19] This document addresses all patients with potentially terminal illness, not just oncology patients. There were five main recommendations:

- Person-centered, family-oriented palliative care should include extra efforts to manage transitions, avoid unneeded hospitalizations, and support family caregivers.
- Clinician–patient communication and advance care planning should be prioritized and improved to ensure that patients have opportunities to articulate their preferences while they are still able to.
- Professional education and development should extend the new discipline of hospice and palliative medicine into medical and nursing school curricula—across professional silos—and it should include improving physician communication skills.
- Policies and payment systems must be reorganized to incentivize care coordination and palliative care provision and to discourage excessive use of inpatient days and multiple care transitions.
- Public education and engagement about end-of-life care is crucial; efforts must be made to normalize conversations about death and dying.

Medicare fails to adequately compensate long outpatient discussions, typical of end-of-life care. Using the 2013 National Medicare Fee Schedule, a physician who spends 35 minutes discussing the lack of benefit of additional cancer-directed therapy and hospice referral received 27% lower compensation than he or she would by seeing two patients for a 15-minute visit entirely dedicated to describing the schedule of administration and side effects of a new line of therapy.[20] During the discussions about the approval and implementation of the Affordable Care Act, there was a proposal to compensate for end-of-life discussions. The goal was to stimulate the counseling of patients and families to avoid futile and expensive care near the end of life. Most medical oncologists likely would agree that discussions about of end-of-life care are critical for our patients, their families, and society in general. In a recent sign of progress, the American Medical Association has released codes for advanced care planning.[20] This is an important step for Medicare to consider the coverage of end-of-life discussions.

GUIDELINES

Choosing Wisely is an American Board of Internal Medicine Foundation initiative supported by more than 60 medical specialties.[21] It aims to promote discussions between providers and patients to achieve care that is "supported by evidence; not duplicative of other tests or procedures already received; free from harm; truly necessary." The American Society of Clinical Oncology (ASCO) has joined Choosing Wisely and proposed two lists with a total of 10 interventions "whose common use and clinical value are not supported by available evidence." The very first of these listed procedures applies to the discussion of palliative chemotherapy not supported by existing evidence:

- "Do not use cancer-directed therapy for solid tumor patients with the following characteristics: low performance status (3 or 4), no benefit from prior evidence-based interventions, not eligible for a clinical trial, and

no strong evidence supporting the clinical value of further anticancer treatment.

- Studies show that cancer-directed treatments are likely to be ineffective for solid tumor patients who meet the above stated criteria.
- Exceptions include patients with functional limitations due to other conditions resulting in a low performance status or those with disease characteristics (e.g., mutations) that suggest a high likelihood of response to therapy.
- Implementation of this approach should be accompanied with appropriate palliative and supportive care."

And in the 2013 List of Recommendations:

- "Do not use a targeted therapy intended for use against a specific genetic aberration unless a patient's tumor cells have a specific biomarker that predicts an effective response to the targeted therapy."

While the ASCO Clinical Practice Guidelines (2011 Focused Update) do not explicitly discourage the further treatment of lung cancer after patients have progressed on first- and second-line therapies, the guidelines stop short of recommending against third- and fourth-line therapy:

- "When disease progresses on or after second-line chemotherapy, treatment with erlotinib may be recommended as third-line therapy for patients with performance status of 0 to 3 who have not received prior erlotinib or gefitinib.
- Data are not sufficient to make a recommendation for or against using cytotoxic drug as third-line therapy; patients should consider experimental treatment, clinical trials, and best supportive care."

CONCLUSION

After years of slow progress, the speed of innovation in advanced NSCLC has increased greatly, with an explosion of new therapies, targeted therapies, and immunotherapies. Although these new options offer great promise for patients, they may also paradoxically increase the risk of ineffective and potentially harmful treatment near the end of life. When there is general pessimism about the role of treatment in advanced lung cancer, it is less likely to be given, either appropriately or inappropriately. As enthusiasm grows for treatment, practicing oncologist struggles to provide those treatments to patients in a way that maximizes potential benefit and minimizes risk. This is a difficult dilemma given the absence of randomized data in the third- and fourth-line settings. However, the available data suggests some principles:

- Every patient with advanced NSCLC should receive early palliative care and advance care planning with regard to end-of-life care. This will reduce the risk of futile and unwanted treatments, has been shown to improve outcomes, and empowers patients to make informed decisions about their care.
- Routine use of cytotoxic chemotherapy in the third and fourth line is not supported by prospective data. Patients with previous response to therapy and continuing good performance status seem most likely to benefit from further lines of therapy.
- For patients with NSCLC, molecular analysis is a necessary component of care and may identify treatment options even after conventional second-line therapy.

The therapy options for patients with NSCLC have greatly expanded. These therapies have improved the overall survival and quality of life of many patients affected by the disease. Their high cost is a challenge to patients, physicians, and society in general. Medical oncologists have the responsibility to gather all evidence to identify therapies likely to benefit and protect patients from the toxicities of ineffective therapies.

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LUNG CANCER

New Therapies for Histologies Other than Adenocarcinoma

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Beyond Adenocarcinoma: Current Treatments and Future Directions for Squamous, Small Cell, and Rare Lung Cancer Histologies

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OVERVIEW

Lung cancer encompasses a diverse spectrum of histologic subtypes. Until recently, the majority of therapeutic advances were limited to the minority of patients with adenocarcinoma. With the advent of comprehensive genomic profiling of squamous and small cell lung cancers, new therapeutic targets have emerged. For squamous tumors, the most promising of these include fibroblast growth factor receptor (FGFR), the phosphatidylinositol 3-kinase (PI3K) pathway, discoidin domain receptor 2 (DDR2), and G1/S checkpoint regulators. In 2014, the antiangiogenic agent ramucirumab was approved for all non–small cell lung cancer (NSCLC) histologies, including squamous tumors. Immunotherapeutic approaches also appear to be promising for these cases. Genomic analysis of small cell lung cancer has revealed a high mutation burden, but relatively few druggable driver oncogenic alterations. Current treatment strategies under investigation are focusing on targeting mitotic, cell cycle, and DNA repair regulation, as well as immunotherapy. Pulmonary neuroendocrine tumors represent a diverse spectrum of diseases that may be treated with somatostatin analogs, cytotoxic agents, and molecularly targeted therapies. Radiolabeled somatostatin analogs and combinations with mammalian target of rapamycin (mTOR) inhibitors also show potential. Large cell neuroendocrine tumors share numerous clinical, pathologic, and molecular features with small cell lung cancer; however, whether they should be treated similarly or according to a NSCLC paradigm remains a matter of debate.

Recent therapeutic advances in lung cancer have been almost exclusively limited to adenocarcinoma histology. Molecular profiling efforts to identify genomic alterations, driver oncogenes, and druggable targets have focused on adenocarcinoma. Until recently, antiangiogenic treatments were limited to nonsquamous NSCLC because of concerns of heightened toxicity (life-threatening hemoptysis) in squamous cases. Additionally, use of the well-tolerated, convenient, and effective cytotoxic agent pemetrexed is also restricted to nonsquamous cases because of inferior outcomes in squamous cases.

Lung cancer encompasses numerous diverse histologic types (Sidebar 1). After decades of inactivity, recent years have seen advances in our understanding and treatment of lung cancer types beyond adenocarcinoma. Genomic alterations that may provide therapeutic targets have been identified in squamous cell carcinoma, and newer antiangiogenic agents appear to be tolerated in this histologic subtype. Gene sequencing efforts in small cell lung cancer have identified one of the highest mutational burdens of any malignancy, and prophylactic cranial irradiation in extensive stage disease has been shown to improve neurologic outcomes and overall survival. Although advances for less common lung tumors, such as large cell carcinoma and bronchial carcinoids, have been hampered by their low frequency and a lack of consensus on disease categorization, recent data suggest that certain molecularly targeted agents, liver-directed therapies, and radiolabeled somatostatin analogs may improve outcomes. This review provides an overview of the current approach and future directions for these diverse malignancies.

SQUAMOUS CELL CARCINOMA

Recently, genotyping efforts—ranging from the comprehensive, such as The Cancer Genome Atlas' squamous lung cancer study, to the individual, such as the characterization of *FGFR1* amplification and *DDR2* mutations— have brought to light a number of putative therapeutic targets that appear to occur in toto in more than half of all patients' tumors. What follows is a summary of recent diagnostic and therapeutic developments aimed at improving the outcomes of patients with this disease.

Squamous tumors account for 20% to 30% of all NSCLC cases.[1] The prototypical squamous cancer is characterized by

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a tumor that is well differentiated and exhibits classic structural features such as keratinization, intercellular bridges, and pearl formation.[1,2] Histopathologic subtypes include papillary, basaloid, clear cell, and small cell variants. Most squamous lung cancers are marked by the expression of p40/p63, cytokeratins 5/6, high molecular weight keratin, and carcinoembryonic antigen. Most cases do not express cytokeratin 7 and thyroid transcription factor 1 (TTF-1).[3]

There are a number of diagnostic challenges inherent to this disease. Small biopsy specimens and poorly differentiated tumors often lack the histologic hallmarks of squamous differentiation. In such cases, immunohistochemical (IHC) profiling for both p40/p63 (positive in squamous cases) and TTF-1 (negative in squamous cases) has been established as a useful approach for determining lineage.[1,3] A number of studies have also addressed the issue of adenosquamous carcinomas, tumors that have most likely arisen from a common clone but exhibit divergence in histologic appearance. In terms of molecular biology, these tumors appear to be more closely aligned with adenocarcinomas than squamous cell carcinomas, which has important therapeutic implications as it relates to current guidelines for *EGFR* and *ALK* testing.[1]

In 2012, The Cancer Genome Atlas published a comprehensive molecular analysis of 178 early-stage squamous lung tumors and, from a conceptual standpoint, ushered in an era of personalized medicine for patients with this disease.[4] These data, coupled with discoveries made by other researchers,[5-7] crystallized the notion that a potentially actionable oncogenic driver could be found in the majority of squamous cases. Key targets are discussed below, and include

KEY POINTS

- Although most recent lung cancer developments have been limited to adenocarcinoma histology, numerous discoveries for squamous, small cell, and other histologies have also been made.
- A putative oncogenic driver can be identified in the majority of patients with squamous cell lung cancer. Key druggable targets include *FGFR1* amplification, PI3K pathway alterations, cell cycle checkpoint disturbances, and *DDR2* mutations.
- Ramucirumab, a monoclonal antibody against VEGFR-2, is now FDA-approved in conjunction with docetaxel for the treatment of patients with non–small cell lung cancers, including squamous cell lung cancers, making this the first antiangiogenesis drug available to patients with this disease.
- Comprehensive genomic analyses of small cell lung cancer have been conducted. Current experimental treatment approaches are focusing on targeting mitotic, cell cycle, and DNA repair regulation, as well as immunotherapy.
- Pulmonary neuroendocrine tumors represent a diverse spectrum of diseases. Radiolabeled somatostatin analogs and molecularly targeted agents are under investigation.

SIDEBAR 1. World Health Organization Classification of Lung Cancers, Including Modification by IASLC/ATS/ERS Classification of Lung Adenocarcinoma[155]

Preinvasive Lesions
- Bronchial squamous dysplasia/carcinoma in situ
- Atypical adenomatous hyperplasia
- Adenocarcinoma in situ
- Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

Adenocarcinoma
- Minimally invasive adenocarcinoma ($\leq$ 3 cm lepidic predominant tumor with $\leq$ 5 mm invasion)
- Invasive adenocarcinoma
  - Lepidic predominant (nonmucinous with > 5 mm invasion)
  - Acinar predominant
  - Papillary predominant
  - Micropapillary predominant
  - Solid predominant with mucin

Adenocarcinoma Variants
- Invasive mucinous adenocarcinoma
- Colloid
- Fetal
- Enteric

Squamous Cell Carcinoma (Variants)
- Papillary
- Clear cell
- Small cell
- Basaloid

Small Cell Carcinoma (Variant)
- Combined small cell carcinoma

Large Cell Carcinoma (Variants)
- Large cell neuroendocrine carcinoma (LCNEC) and Combined LCNEC
- Basaloid carcinoma
- Lymphoepithelioma-like carcinoma
- Clear cell carcinoma
- Large cell carcinoma with rhabdoid phenotype

Adenosquamous Carcinoma

Sarcomatoid Carcinoma
- Pleomorphic carcinoma
- Spindle cell carcinoma
- Giant cell carcinoma
- Carcinosarcoma
- Pulmonary blastoma

Carcinoid Tumor
- Typical carcinoid
- Atypical carcinoid

Salivary Gland Tumors
- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Epithelial-myoepithelial carcinoma

Abbreviations: IASLC, International Association for the Study of Lung Cancer; ATS, American Thoracic Society; ERS, European Respiratory Society.

FGFR1 amplification, alterations in the PI3K pathway, *DDR2* mutations, and cell cycle checkpoint dysregulation. Many of these alterations are therapeutic targets in Lung-MAP (S1400, NCT02154490), a multi–sub-study randomized phase II trial concept sponsored by the Southwest Oncology Group (SWOG) that is designed to screen and match patients to rationally selected therapies based on tumor molecular profiling. Importantly, many of the genomic alterations identified in squamous lung tumors do not appear to be mutually exclusive (in contrast to the better known alterations in lung adenocarcinoma such as *EGFR* and *KRAS* mutations and *ALK* rearrangements). This will likely complicate the interpretation of efficacy data from treatments directed against single targets (Fig. 1). This section also discusses two novel therapies—ramucirumab, a monoclonal antibody against vascular endothelial growth factor receptor (VEGFR), and necitutumab, a monoclonal antibody against epidermal growth factor receptor (EGFR). These agents have demonstrated significant, although modest, efficacy in randomized phase III trials when combined with chemotherapy. Finally, this section reviews the role of immunotherapy, which has emerged as a distinct therapeutic category of substantial clinical importance for squamous lung cancer.

Fibroblast Growth Factor Receptor 1

The FGFR family consists of four transmembrane receptor tyrosine kinases that participate in the regulation of embryonal development, proliferation, differentiation, and angiogenesis. FGFR1, FGFR2, FGFR3, and FGFR4 bind variably to 22 mitogenic and hormonal ligands. Upon ligand binding, FGFR undergoes dimerization and activates downstream signaling via the phosphatidylinositol 3-kinase (PI3K), RAS/RAF/MAPK, and protein kinase C (PKC) pathways. Alterations in FGFR1–4 were detected in 27% of squamous tumor samples reported by The Cancer Genome Atlas, with *FGFR1* amplification the most common event (17% of cases).[8] Although *FGFR1* amplification is considered an oncogenic event, there is variability in the correlation between gene amplification, mRNA expression, and protein expression in cell lines and tumors.[7,9,10] This is a key point, as not all *FGFR1*-amplified cell lines and xenografts respond to FGFR inhibi-

tors.[9,10] In addition, less common mutations in *FGFR1–4* and fusion events with BAG4 and TACC3 have been identified that may, as in other malignancies, predict for response to FGFR inhibition.[4,11]

A few studies have looked at the prognostic implications of *FGFR1* amplification in early-stage disease. In a study by Kim et al, Asian patients with surgically resected squamous lung tumors that harbored *FGFR1* amplification were more often current smokers and had worse overall survival (OS) than those without amplification (51 vs. 115 months; p = 0.002).[12] In contrast, North American patients with *FGFR1*-amplified squamous tumors were found to have no distinct clinical characteristics and no survival disadvantage.[13]

A number of FGFR-specific small molecular inhibitors have been or are being tested in phase I and phase II trials, including BGJ398 (NCT01004224, NCT02160041), AZD4547 (NCT00979134, NCT02154490), and JNJ-42756493 (NCT01703481). All three compounds have low nanomolar IC50s for kinase inhibition against FGFR1, FGFR2, and FGFR3; additionally, JNJ-42756493 has low nanomolar specificity for FGFR4. An FGF ligand trap, GSK3052230, is also being studied in combination with chemotherapy (NCT01868022). Toxicities associated with the small molecule inhibitors include stomatitis, asthenia, nausea/vomiting, corneal/retinal changes, and transaminitis. In addition, hyperphosphatemia, which is an on-target effect of these drugs, is relatively common. Preliminary efficacy data have been presented from patients with advanced squamous lung cancer who were treated with BGJ398[14] and AZD4547.[15] Overall response rate (ORR) ranged from 8% with AZD4547 to 15% with BGJ398; survival data have not yet been presented. Given the modest responses seen with these drugs, additional work will be required to define better predictors of response, including genomic covariates and other markers of FGFR1 pathway activation.

Phosphatidylinositol 3-Kinase Pathway

The PI3K pathway is an intracellular signal transduction pathway for many upstream receptor tyrosine kinases and regulates cell survival, metabolism, motility, and angiogenesis. Abnormalities in this pathway are more common in lung

FIGURE 1. Oncoprint of Selected Oncogenes and Tumor Suppressors from 178 Resected Squamous Cell Lung Cancers Analyzed by the Cancer Genome Atlas[153]
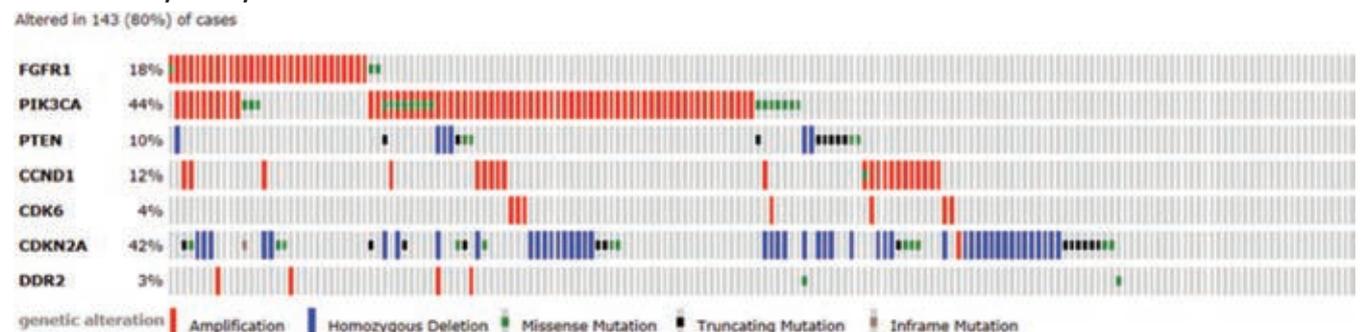
Note the substantial degree of target overlap for many of these patients.

squamous carcinoma than in lung adenocarcinoma, which suggests that there may be an increased dependence on this pathway in squamous tumors.[16-18] This observation is underscored by recent in vivo modeling, in which biallelic inactivation of PTEN and LKB1 led to spontaneous squamous lung tumor formation.[19] Alteration in one of the components of the PI3K pathway was observed in 47% of tumors analyzed by The Cancer Genome Atlas.[8] PIK3CA mutations, predominantly in the catalytic and regulatory domains, occur in approximately 10% of cases,[4] with PIK3CA amplification accounting for 40% of these.[4,18] Complete PTEN loss by IHC was found in 24% of cases,[20] and PTEN was also found to be mutated in 7% of tumors.[4]

Preclinical studies have provided a rationale for targeting upstream PI3K pathway alterations with novel therapies. In particular, squamous tumor cell lines and mouse models harboring PIK3CA mutations or gene amplification and PTEN loss are sensitive to PI3K inhibitors.[21,22] There are a number of ongoing or completed early phase trials of PI3K-alpha specific inhibitors or dual PI3K-alpha/mTOR inhibitors for patients with advanced squamous lung cancer, including studies of GDC0032 (NCT02154490), BKM120 (NCT01297491), and LY3023414 (NCT01655225). To date, no efficacy data have been presented from these trials.

Discoidin Domain Receptor 2

Discoidin domain receptor 2 (DDR2) is a receptor tyrosine kinase that regulates cell adhesion, proliferation, and extracellular remodeling upon binding to its endogenous ligand, type 1 collagen.[23,24] The potential importance of DDR2 mutations in squamous lung cancer was established by Hammerman et al, who found an overall mutation rate of 3.8% in this gene and demonstrated that certain mutations lead to gain-of-function phenotypes that can be reversed with dasatinib, a multikinase inhibitor with activity against both DDR1 and DDR2.[5] Two prior early-phase studies of dasatinib alone or in combination with erlotinib in patients with advanced NSCLC showed little overall efficacy.[25,26] However, one patient with a squamous tumor harboring a DDR2 S768R mutation that was EGFR wild-type achieved a partial response to dasatinib plus erlotinib.[5] A partial response to dasatinib was also reported in a patient with synchronous chronic myelogenous leukemia and an early-stage squamous lung tumor bearing a DDR2 S768R mutation.[27] Given the sporadic nature of DDR2 mutations and limited preclinical data about their functionality, it is unclear what proportion of DDR2 mutant squamous patients might benefit from dasatinib. A phase II study of dasatinib in DDR2 mutant squamous lung cancer was recently terminated as a result of poor accrual (NCT01514864). Additional clinical data will likely rest on the development of a DDR2-specific inhibitor or on case reports of off-label use of dasatinib.

G1/S Checkpoint Inhibition

Cell division, formalized in the various phases of the cell cycle that move the cell from a state of quiescence (G0) to DNA synthesis (G1, S) and ultimately mitosis (G2, M), is an intri-

cately controlled process that depends on a series of negative regulatory mechanisms to ensure replication fidelity and maintenance of homeostasis. These mechanisms can be bypassed through the dysregulation of a handful of cell cycle checkpoint suppressors such as retinoblastoma (RB), P53, and p16 and activators such as the cyclin/cyclin-dependent kinase (CDK) complexes. Cyclins D1–3, which bind to CDKs 2, 4, and 6, are important early regulators under the control of mitogenic signaling. These complexes phosphorylate the tumor suppressor RB, which facilitates dissociation of RB from E2F transcription factors. In turn, E2F activation leads to a transcriptional program that moves the cell from G1 to the S phase.[28]

G1/S checkpoint regulators are commonly altered in squamous tumors.[4] CCND1, which encodes cyclin D1, is amplified in 13% of cases, and CDK6 is amplified in 4%. CDKN2A, which encodes the tumor suppressor p16 that inhibits CDK4 and 6, is mutated or homozygously deleted in 45% of tumors. The frequency of these aberrations has made targeting the cell cycle an attractive concept, although there are limited published preclinical and clinical data to support this strategy.[29-31] Palbociclib, which received U.S. Food and Drug Administration (FDA) approval for use in combination with letrozole for patients with advanced hormone receptor-positive breast cancer, is also being studied in advanced squamous cell lung cancer positive for CCND1 amplification, CDK6 amplification, or CDKN2A deletion/mutation (NCT02154490).

Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) are key mediators of angiogenesis.[32] Bevacizumab, a monoclonal antibody against VEGF, is FDA approved for the treatment of nonsquamous NSCLC. It is not approved for patients with squamous NSCLC because of safety concerns centered on hemoptysis, which is now thought to be fueled by the common anatomic distribution of this disease (i.e., central cavitary tumors that may abut or invade local vascular structures) rather than any unique intrinsic biologic characteristic.[33-35] Nevertheless, squamous cases were included in the recently published REVEL study, which randomly assigned patients with advanced NSCLC to receive docetaxel with or without the anti–VEGFR-2 monoclonal antibody ramucirumab. The addition of ramucirumab to chemotherapy demonstrated an improvement in overall survival (median OS 10.5 versus 9.1 months; hazard ratio [HR] 0.86, p = 0.02), progression-free survival (PFS, HR 0.76, p < 0.0001), and ORR (23% vs. 14%, p < 0.0001) favoring addition of ramucirumab. There was no disproportionate increase in bleeding events for patients with squamous tumors.[36] Ramucirumab plus docetaxel is now FDA approved for patients with previously treated advanced NSCLC, regardless of histologic subtype.

Epidermal Growth Factor Receptor

The epidermal growth factor receptor (EGFR) is a well-characterized proto-oncogene that, when mutated, engenders a state of oncogene addiction that has been successfully

targeted by small molecular inhibitors.[37,38] The role of wild-type protein overexpression as a target for therapy has been less clear. Both squamous cell cancers and adenocarcinomas are marked by high levels of EGFR expression, although this does not predict sensitivity to EGFR tyrosine kinase inhibitors.[39] Cetuximab, a chimeric monoclonal antibody against EGFR, has efficacy when coupled with chemotherapy in patients with advanced NSCLC.[40] Additionally, a subset analysis showed that patients with squamous cancers that highly expressed EGFR had a significant improvement in OS that favored the cetuximab combination (HR 0.62; 95% CI, 0.43 to 0.88), providing an impetus to study this strategy further.[41] More recently, a randomized phase III trial of cisplatin plus gemcitabine with or without necitumumab, a fully human anti-EGFR monoclonal antibody, showed a significant, though modest, improvement in OS with the addition of necitumumab (median OS 11.5 vs. 9.9 months favoring necitumumab, HR 0.84, p = 0.01). EGFR expression did not predict for therapeutic benefit. Despite the OS benefit, there was minimal improvement in PFS (5.7 vs. 5.5 months, p = 0.020) and ORR (31% vs. 29%, p = 0.4).[42]

Immunotherapy

After decades of efforts to develop cancer immunotherapies, treatments directed against the checkpoints that negatively regulate the adaptive immune response have recently shown promising efficacy across a wide range of malignancies, including lung cancers. Most of this activity is centered on the inhibitory programmed death protein 1 (PD-1), which is expressed on T cells and attenuates T-cell activation upon binding to programmed death-ligand 1 (PD-L1) and PD-L2.[43] A number of monoclonal antibodies against PD-1 or PD-L1 are in clinical development in lung cancer, including nivolumab, pembrolizumab, MEDI4736, and MPDL3280A. Although the initial data for some of these drugs showed heightened activity in patients with squamous lung cancers, subsequent data have shown that histology by itself is not a predictor of response. Instead, PD-L1 expression has emerged as a potentially informative biomarker, with ORRs of between 20% and 30% in patients with PD-L1$^+$ tumors. Notably, a subset of patients have experienced durable responses to treatment captured in the "tails" of the overall survival curves that have been presented, underscoring the need for better predictors of response to these agents.[44-46] Both nivolumab and pembrolizumab have received accelerated FDA approval for the treatment of advanced melanoma and several clinical trials are ongoing in lung cancer.

SMALL CELL LUNG CANCER

Small cell lung cancer (SCLC) is a highly malignant neoplasm representing less than 15% of all lung cancers. It is strongly associated with cigarette smoking. Traditionally the disease has been classified as either limited stage (LS, 20% of cases) or extensive stage (ES). "Limited" refers to the fact that the disease can be encompassed within one radiation portal. The

use of the tumor, node, metastasis staging system staging for SCLC has been recently advocated given the fact that within the LS category differences in survival can be seen within stages I, II, and III. In rare cases (less than 1%) SCLC may present as a small peripheral nodule and be amenable to surgical resection. Despite this, analysis of the National Lung Cancer Screening Trial using low-dose CT showed no benefit in the subgroup that was diagnosed with SCLC, indicating the lack of an effective screening strategy for this disease.[47] SCLC may present with elements of NSCLC. This "combined SCLC" entity may be under-reported because of limited tissue sampling availability in many cases.[48] The treatment approach for LS-SCLC is combined modality therapy, with hyperfractionated radiation being superior to standard fractionation and early radiation being better than late radiation.[49-51] For ES-SCLC, systemic chemotherapy is the standard approach, with platinum (either cisplatin or carboplatin) combined with etoposide being the most commonly used treatment. Prophylactic cranial radiation is used for both LS and ES disease and has been shown to decrease relapses in the brain and increase survival.[52,53] However, in a recently reported large Asian trial, PCI appeared to have a detrimental effect on OS in ES-SCLC.[54] Whether this reflects differences in study design, treatment, or populations is not clear. Most recently, the use of consolidation thoracic radiation for ES-SCLC has been shown to confer some benefit.[55] Unfortunately, apart from a proportion of patients with LS-SCLC, all patients will ultimately relapse and second-line therapy is generally ineffective, although topotecan has been approved for this setting. The above data indicate there has been very little improvement in the management of SCLC over the past 3 decades.

Understanding the Biology of SCLC to Find Better Therapies

Figure 2 depicts many, but not all, of the molecular changes seen in SCLC. Alterations in p53, RB, and Myc remain the most frequent. Unfortunately, so far none of these alterations has been amenable to drug targeting. Recently, two publications have comprehensively analyzed the genomics of SCLC.[56,57] These studies collectively showed frequent amplification of *SOX2* as well as recurrent mutations in *CREBBP, EP300,* and *MLL,* three genes that are involved in histone modifications. A major limitation of these studies is that the majority of samples were from patients with resected disease, which is known to be uncommon and may demonstrate a somewhat different biology. This limited access to tissue may be circumvented with novel technology allowing genetic profiling of circulating tumor cells in SCLC.[58] Whole-genome analysis of a single patient with stage IA SCLC also showed copy gains in *hTERT,* a catalytic subunit of the enzyme telomerase.[59]

Clinical Trials in SCLC

Sidebar 2 depicts many, but not all, of the targets that have recently been studied or are the subject of ongoing trials in

FIGURE 2. Overview of Small Cell Lung Cancer Biology
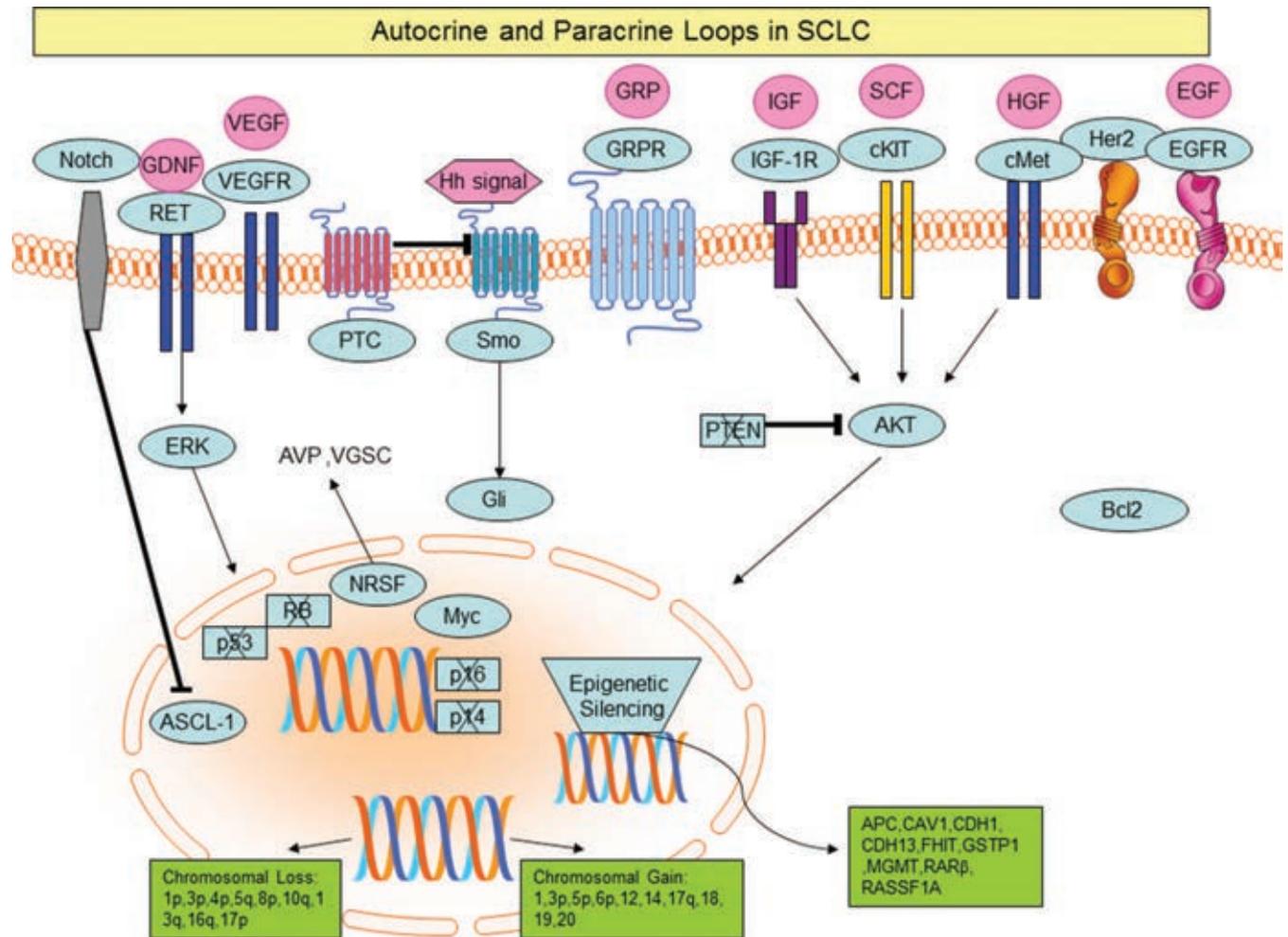
A number of constitutively active signal transduction pathways have been identified. At the nuclear level a number of tumor suppressor genes (denoted by boxes) are inactivated (X within the box). In addition, a number of dominant oncogenes (denoted by the oval shape) are overexpressed, including transcription factors. The antiapoptotic protein Bcl2 is commonly overexpressed in SCLC. Chromosomal gains and loss are common in SCLC. Increased telomerase activity is commonly seen, as well as epigenetic silencing of a number of important genes.

SCLC. Proteins associated with mitotic regulation have been prime targets for drug development. Based on a single-arm study of the aurora kinase inhibitor alisertib, which yielded a 27% response rate in predominantly refractory patients, a randomized phase II trial has been launched. We have also recently demonstrated that 40% to 50% of SCLC cell lines are highly sensitive to low nanomolar concentrations of polokinase inhibitors.[60] Preclinical data suggest that targeting both polokinase and aurora kinases may be particularly effective in tumors with amplification of *Myc*.[61] Studies of polokinase inhibitors in SCLC have yet to be started. Targeting the cell cycle regulatory proteins is also of interest. Our comprehensive drug analysis showed CDK inhibition as a promising target; indeed, a very recent publication has shown that THZ1, a covalent inhibitor of CDK7, is highly potent in SCLC models.[62]

Another attempt to find better therapies for SCLC includes identification of subgroups of SCLC harboring unique oncogenic drivers amenable to targeting. Although a variety of NSCLC subgroups with different oncogenic mutations (e.g., *EGFR*, *ALK*, *RAS*) have been identified, this has not been the case for SCLC. We have recently identified an oncogenic *RET* mutation in SCLC that shows great susceptibility to RET inhibitors in vitro.[63] *RET* mutations may be present in 1% to 2% of patients with SCLC. In addition, a high expression level of wild type *RET* also seems to confer some sensitivity to RET inhibitors. Other investigators have identified frequent changes in the PI3K/AKT/mTOR pathway, including *PTEN* loss, *RICTOR* amplification, and *PIK3CA* mutation. The relevant cell lines showed sensitivity to the dual TORC1/2 inhibitor BEZ235.[64] Anther potential SCLC subgroup with a unique driver may be those cases with *FGFR* amplification.[61] Genomic analysis by Rudin et al showed *FGFR1* amplification in 6% of SCLCs.[56] At the protein level, increases in PARP are commonly seen, and preclinical data shows efficacy of PARP inhibition in animal models.[65] Trials of a PARP inhibitor (veliparib) in conjunction with front-line platinum-based chemotherapy or second-line temozolomide are ongoing.

As with other cancers, there is great interest in determining whether immunotherapy might play a role in the management of SCLC. Many trials of vaccine-based approaches have

failed. Clinicians have long observed that patients with SCLC and autoimmune complications (e.g., paraneoplastic neurologic syndromes) have a better prognosis.[66] Thus, studies of the checkpoint inhibitors of cytotoxic T lymphocyte antigen-4 (CTLA-4) and PD-1/PD-L1 are of great interest and are either ongoing or completed. A randomized phase II trial of phased ipilumumab combined with chemotherapy showed improvements in PFS.[67] A phase III trial of this agent in conjunction with chemotherapy has been completed. Analysis of SCLC samples showed no PD-L1 protein expression by immunohistochemistry in SCLC tumor cells; however, 18% of tumors had PD-L1–positive intratumoral macrophages and 48% had PD-L1–positive infiltrating lymphocytes within the tumor.[68]

In conclusion, these are exciting times for SCLC clinical research. First and foremost, pharmaceutical companies are taking notice of the disease. Second, we are finally approaching SCLC based on its biology and not empirical drug devel-

opment. Third, trial design in SCLC is improving. Phase II randomization is necessary in most settings before moving a drug to phase III clinical trials.[69]

RARE LUNG CANCER HISTOLOGIES

Aside from squamous cell carcinoma and small cell lung cancer, the other nonadenocarcinoma lung cancers are quite rare. As shown in Sidebar 1, the World Health Organization (WHO) organizes these malignancies into the categories of large cell carcinoma, sarcomatoid carcinoma, carcinoid tumors, and salivary gland tumors. Because sarcomatoid features do not necessarily affect disease management, and salivary gland tumors are most commonly considered a category of head and neck cancer, this section focuses on well-differentiated neuroendocrine (carcinoid) tumors and large cell carcinoma variants. Because there have been relatively few recent advances in the treatment of these malignancies and their existing management strategies are complex and nuanced, this section provides an overview of standard treatment as well as new developments.

The Spectrum of Neuroendocrine Lung Tumors

The spectrum of neuroendocrine lung malignancies includes well-differentiated (typical and atypical carcinoid) and poorly-differentiated (large cell neuroendocrine cancer and small cell cancer) cancers. Neuroendocrine tumors (NETs) arise from specialized peptide- and amine-producing neuroendocrine cells (Kulchitsky cells) that have migrated from the embryologic neural crest. These cells can take up and modify amine precursors such as L-dOPA or 5-hydroxytryptophan. Among well-differentiated NETs, the gastrointestinal tract accounts for two-thirds of cases and the lung one-third of cases, with rare cases occurring in the thymus or ovary.[70-72] The incidence of NETs in the United States has increased over time, a trend that has been attributed to greater use of advanced imaging techniques that detect a greater number of asymptomatic tumors and to improved classification.[71,73,74] Because many of these cancers are indolent and have prolonged survival even in advanced stages, the prevalence of neuroendocrine cancers in the United States now exceeds 100,000.[73] SCLC (14% of all lung cancers, discussed previously) is by far the most common pulmonary neuroendocrine cancer, followed by large cell neuroendocrine (3%), typical carcinoid (2%), and atypical carcinoid (0.2% to 0.5%). Pathologically, these cancers differ by morphologic features, proliferative markers, and hormonal secretory function (Table 1). Well-differentiated pulmonary neuroendocrine tumors (typical and atypical carcinoid) may arise in a background of diffuse idiopathic pulmonary neuroendocrine hyperplasia (DIPNECH), an intramucosal proliferation of bland neuroendocrine cells that is confined within bronchial and bronchiolar basement membranes and is associated with varying degrees of airway fibrosis.[75-77] SCLC and

TABLE 1. Features of Neuroendocrine Lung Tumors[155]

	Typical Carcinoid	Atypical Carcinoid	LCNEC	SCLC
NE Features	Well differentiated	Well differentiated	Poorly differentiated	Poorly differentiated
Cell Size	Intermediate	Intermediate	Large to Intermediate	Small to Intermediate
Mitotic Rate	Low	Intermediate	High	High
	< 2 mitoses/2 mm^2	2-10 mitoses/2 mm^2	Median 70 mitosis/2 mm^2	Median 80 mitoses/2 mm^2
NE Markers by IHC	+++	++ to +++	+ to +++	±
Necrosis	-	+ (focal)	+++	+++
KI-67 Index	≤ 5%	5-20%	50-100%	80-100%
5-yr survival	90-95%	60-70%	10-40%	≤5-10%

Abbreviations: IHC, immunohistochemistry; LCNEC, large cell neuroendocrine carcinoma; NE, neuroendocrine; SCLC, small cell lung cancer.
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large cell neuroendocrine carcinoma do not have identified precursor lesions. Advancing across the pulmonary neuroendocrine spectrum, patient age and smoking rates increase. The average age at diagnosis is age 45 for typical bronchial carcinoids, approximately age 55 for atypical carcinoids, and age 60 to 65 for large cell neuroendocrine tumors.[78-81] Between one-third and two-thirds of patients with well-differentiated tumors are smokers, and these rates may be higher among patients with atypical carcinoids than those with typical carcinoids.[70,78,82,83] Similar to SCLC, more than 85% of patients with large cell neuroendocrine cancer have a history of smoking.[80,81] No other known carcinogens have been linked to carcinoid. Ten percent of bronchial NETs are hereditary (multiple endocrine neoplasia 1 [MEN1]). In contrast to other lung tumors (which are more common in males than females) and other neuroendocrine tumors (which have equal prevalence in males and females), bronchial carcinoids are more common in females.[70,82] Low- and intermediate-grade NETs are further divided into functional (secretory) or nonfunctional (nonsecretory) groups depending on whether there is evidence of a hormone-related clinical syndrome.

Well-Differentiated Neuroendocrine Cancers (Typical and Atypical Carcinoid)

More than 85% of typical bronchial carcinoids are stage I at presentation, and more than 50% of atypical carcinoids present as stage II or III. Approximately 2% of patients with typical carcinoid and 20% with atypical carcinoid will have distant metastatic disease at presentation.[82] Classic teaching purports that, unlike many gastrointestinal NETs from which venous blood flow passes through portal circulation, bronchial neuroendocrine tumors do not require a high burden of liver metastases to cause a clinical carcinoid syndrome. Nevertheless, because of the frequent lack of aromatic amino acid decarboxylase, resulting in lower production of serotonin and its metabolites,[84] carcinoid syndrome is rarely encountered in localized disease and only with large (>5 cm) primary tumors.[85] As such, wheezing at presentation is more likely to be caused by anatomic obstruction than secretion of

bioactive substances. Furthermore, because the risk of carcinoid crisis is considerably lower than with gastrointestinal carcinoids,[86,87] prophylactic treatment with octreotide before biopsy or resection is not typically recommended, although it may be considered before liver-directed therapy. Bronchial carcinoids with liver metastases are associated with carcinoid syndrome in more than 80% of cases.

Clinical features of carcinoid syndrome (flushing, wheezing, diarrhea) have considerable overlap with normal physiology, and may be atypical in cases of bronchial carcinoids. In contrast to physiologic flushing, which tends to involve the entire body, carcinoid flushing has been described as particularly apparent in the face, neck, upper torso, and the palms of the hands or soles of the feet. It is unlikely to be accompanied by diaphoresis. Whereas patients with midgut primaries have typical flushes lasting several seconds to several minutes, those with foregut (including bronchial) primaries may have atypical episodes that last minutes to hours and also feature periorbital edema, disorientation, lacrimation, salivation, hypotension, and tachycardia. In the setting of localized disease, carcinoid syndrome typically resolves after curative resection. For advanced disease, somatostatin analogs such as octreotide (described later) are highly effective. Less commonly (in 1% to 2% of cases), bronchial carcinoids (which are the most common cause of ectopic adrenocorticotropic hormone [ACTH] secretion) may associate with paraneoplastic Cushing Syndrome, which often has acute onset and presents with refractory profound hypokalemia and hypertension.[88-91] Treatment is directed at inhibiting adrenal function and includes high-dose ketoconazole, aminoglutethimide, metyrapone, mitotane, mifepristone, and adrenalectomy.[92] Although this is quite a rare occurrence, bronchial carcinoid is also the most common cause of extrapituitary growth hormone releasing hormone (GHRH), which can result in acromegaly.[93,94]

Diagnostic Evaluation

In 75% of cases, bronchial carcinoids are centrally located and amenable to bronchoscopic biopsy. Atypical carcinoids are more likely to present as peripheral lesions appropriate

for percutaneous biopsy. Computed tomography provides excellent characterization of central lesions (which can be intraluminal, extraluminal, or have components of both). Typically, these appear as well-defined tumors with diffuse or punctate calcification.[95] Because neuroendocrine tumors are highly vascular and can appear isodense with liver on conventional CT depending on contrast phase, multiphase CT or MRI should be used to evaluate liver metastases. High-affinity somatostatin receptor is expressed by the majority of well-differentiated neuroendocrine tumors (80% of typical carcinoids and 60% of atypical carcinoids).[96-98] Accordingly, these tumors may be imaged with the radiolabeled octreotide analog ^{111}In-DTPA-octreotide (somatostatin receptor scintigraphy [SRS], OctreoScan), although this technique has limited specificity because of uptake in other tumor types, granulomas, and autoimmune disease,[84,99-101] SRS may be used both to assess sites of metastases and to assess somatostatin receptor status if treatment with octreotide or lanreotide is considered. However, SRS may have a limited role in cases of apparently localized typical bronchial carcinoid given the low rate (5%) of distant metastases at presentation and improvements in cross-sectional imaging.[70,102] Tumor histology generally predicts which nuclear medicine scan will be clinically useful: SRS for low grade (typical carcinoid); SRS and fluorodeoxyglucose positron emission tomography (FDG-PET) for intermediate grade (atypical carcinoid); FDG-PET for high grade (large cell neuroendocrine, SCLC).

Iodine-meta-iodobenzylguanidine (MIBG) scanning detects the presence of catecholamine transporter proteins expressed by almost all pheochromocytomas, two-thirds of intestinal NETs, and one-third of bronchial NETs. If uptake is evident, I-131 MIBG therapy may be considered.

Numerous biochemical tests may be incorporated into the diagnosis and surveillance of NETs, particularly well-differentiated subtypes. When available, the following markers may be considered selectively according to histologic grade: blood serotonin, 24-hour urine 5-hydroxyindoleacetic acid (5HIAA; >6 mg/24 hours), chromogranin A, pancreastatin (a CgA subunit that tends not to be elevated in nonmalignant conditions), neurokinin A, neuron-specific enolase for well-differentiated NET or "carcinoid"; chromogranin A, neuron-specific enolase for intermediate-grade NET or "atypical carcinoid"; neuron-specific enolase for high-grade or poorly differentiated NET. Serum chromogranin A (CgA), which is elevated in 75% of bronchopulmonary carcinoids but lacks specificity, and 24-hour urine 5HIAA, which is specific but not sensitive, are the most frequently used in clinical practice but are subject to interference from several other conditions and ingestions (Sidebar 3). Given their lack of specificity, these biomarkers have greater utility in disease surveillance than in aiding diagnosis.[102] In particular, CgA levels are lower with bronchial carcinoids than with NETs at other sites and frequently overlap with nonmalignant conditions.[104] Although biomarker pro-

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SIDEBAR 3. Factors That Can Modify Chromogranin A and Urine 5-Hydroxyindoleacetic Acid[156,157]

Elevated Chromogranin A

· Gastroenteropancreatic neuroendocrine tumors
  - GI tract (carcinoid tumors)
  - Pancreatic NETs (islet cell tumors [e.g., gastrinomas, VIPomas, somatostatinomas, glucagonomas, non-functioning neuroendocrine tumors])
· Endocrine disease: hyperparathyroidism, hyperthyroidism, pheochromocytoma, pituitary tumors, medullary thyroid carcinoma
· GI disorders: chronic atrophic gastritis, chronic hepatitis, colon cancer, hepatocellular carcinoma, inflammatory bowel disease, irritable bowel syndrome, liver cirrhosis, pancreatic adenocarcinoma, pancreatitis
· Cardiovascular disease: acute coronary syndrome, arterial hypertension, cardiac insufficiency/failure, essential hypertension, giant cell arteritis
· Drugs: proton pump inhibitors, histamine-2 receptor antagonists
· Inflammatory disease: airway obstruction in smokers, chronic bronchitis, systemic rheumatoid arthritis, systemic inflammatory response syndrome
· Renal disorders: renal insufficiency/failure
· Non-gastrointestinal cancers: breast, ovarian, prostate, small cell lung, neuroblastoma

Urine 5HIAA

· Foods to avoid 48 hours prior to testing: avocados, bananas, cantaloupe, eggplant, pineapple, plums, tomatoes, hickory nuts/pecans, plantains, kiwi, dates, grapefruit, honeydew, walnuts
· Avoid coffee, alcohol, smoking
· Medications that can increase 5HIAA: acetaminophen, ephedrine, diazepam, nicotine, glyceryl guaiacolate (found in some cough medicines), phenobarbital
· Medications that can decrease 5HIAA: corticotrophin, ethanol, imiprimine, levodopa, MAO inhibitors, phenothiazines, aspirin, isoniazid, gentisic acid, methenamine, streptozocin, heparin, methyldopa

Abbreviations: 5HIAA, urine 5-hydroxyindoleacetic acid.

gression may precede radiographic progression by up to 6 to 12 months, intrinsic variance in biomarker levels requires confirmation of increasing concentrations.

Treatment

Well-differentiated bronchial NETs are staged in the same fashion as more common lung carcinomas. For early-stage disease, the principal goal of treatment is curative en bloc surgical resection with negative margins and maximal preservation of lung function. Although a number of bronchoplastic techniques such as sleeve, wedge, and flap resections to avoid lobectomy and larger operations have been described,[105-108] extraluminal tumor components usually preclude such approaches. Unless medically contraindicated, lobectomy and lymph node dissection are generally considered the optimal operation for these cancers, as for other lung tumors,[109,110] although some experts support more limited resections (wedge resection or segmentectomy) for peripheral typical carcinoids given the low likelihood of local recurrence.[111] Endobronchial management, such as bronchoscopic resection with neodymium yttrium aluminum garnet (Nd-YAG) laser and cryotherapy, may be considered for central tumors in medically inoperable patients.[112-114] Recommendations regarding adjuvant therapy are confounded by a lack of applicable high-level data and disagreement among disease experts. Although adjuvant therapy (e.g., platinum/etoposide) is recommended by the National Comprehensive Cancer Network (NCCN) for resected stage II or III atypical carcinoid and for stage IIIB typical carcinoid, postoperative chemotherapy is not recommended by the North American Neuroendocrine Tumor Society (NANETS). Both groups recommend observation alone for resected stage I-III typical carcinoid. Thoracic radiation therapy may have a role for atypical carcinoids with residual disease after surgery and for stage III locally advanced tumors not amenable to resection.[115,116]

Systemic therapy of metastatic well-differentiated NETs may include octreotide, chemotherapy, and molecularly targeted therapies. Because of the lack of prospective trials for bronchial NETs, most recommendations come from either retrospective series or extrapolation from experience with clinical trials primarily enrolling gastrointestinal NETs. A proposed approach to treatment is as follows: (1) Low-grade tumor without hormonal syndrome: consider observation with tumor markers and radiographic studies every 3 to 12 months or somatostatin analog (octreotide, lanreotide) if SRS-positive; (2) Low-grade tumor with hormonal syndrome: somatostatin analog; (3) Intermediate-grade tumor without hormonal syndrome: cytotoxic agents or targeted therapies (see below); (4) Intermediate-grade tumor with hormonal syndrome: somatostatin analog plus cytotoxic agents or targeted therapies; (5) High-grade tumor: platinum/etoposide combination chemotherapy. If there is no response to therapy, one may consider subsequent treatment with a regimen for a lower grade tumor.

The somatostatin analog octreotide is available in a short-acting formulation (typically dosed 150 to 250 mcg subcutaneously three times daily) and a long-acting depot formulation (octreotide LAR) dosed 20 to 30 mg intramuscularly monthly. Before initiating long-acting octreotide, a test dose (50 to 100 mcg) of short-acting octreotide to evaluate for allergic reaction may be considered. Short-acting octreotide may also be continued for 10 to 14 days after initiation of octreotide LAR while therapeutic levels are achieved. Approximately one-third of patients will have breakthrough carcinoid syndrome symptoms that cluster the week before LAR dosing, requiring supplementation with short-acting octreotide. Octreotide controls symptoms in about two-thirds of cases of carcinoid syndrome and can slow tumor growth and provide prolonged periods of disease stabilization, although radiographic regression is rare.[117] Evidence for the therapeutic benefit of somatostatin analogs comes from two studies of metastatic intestinal or pancreatic NETs. In the PROMID study, median time to progression was 14.3 months with octreotide LAR versus 6 months with placebo; cross-over was allowed at progression, and there was no significant difference in OS (not reached in octreotide arm versus 84 months in placebo arm).[118] In the CLARINET study of nonfunctioning locally advanced pancreatic or intestinal NETs, median PFS was not reached in the lanreotide arm (currently approved only for acromegaly in the United States) versus 18 months with placebo (HR 0.47).[119] Analogous to use of gonadotropin releasing hormone (GnRH)–modifying agents in metastatic prostate cancer, somatostatin analogs are continued regardless of disease progression because carcinoid syndrome symptoms remain at least partly responsive to these agents. Adverse effects of chronic somatostatin analog therapy include steatorrhea and cholelithiasis.

Multiple cytotoxic agents may be considered for well-differentiated NETs, including temozolomide, capecitabine, 5-FU, dacarbazine, doxorubicin, and platinum-etoposide (although this last option is generally reserved for higher-grade tumors.[120-125] 5-FU combinations with streptozocin, doxorubicin, or dacarbazine plus epirubicin have yielded response rates in fewer than 20% of patients.[122,123] Capecitabine has been combined with oxaliplatin (response rate 30% in well-differentiated NETs) and with liposomal doxorubicin.[126-128] The efficacy of temozolomide was recently reported in a retrospective study of 31 patients with progressive metastatic bronchial carcinoid (14 typical, 15 atypical, 2 not classified): 14% achieved partial response (PR) and 52% stable disease (SD); median PFS was 5.3 months; median OS was 23.2 months.[129]

The mammalian target of rapamycin (mTOR) inhibitor everolimus was evaluated in the RADIANT-2 phase III trial, in which 429 patients with advanced neuroendocrine tumors and carcinoid syndrome were randomly assigned to octreotide LAR with everolimus or placebo.[130] Median PFS was 16.4 months versus 11.3 months, respectively (p = 0.03). In a

subgroup analysis of the 44 patients with bronchial carcinoid (33 received everolimus plus octreotide; 11 received placebo plus octreotide), median PFS was 13.6 months versus 5.6 months.[131] Almost 50% of patients treated with everolimus had grade 3 or 4 adverse events (most commonly diarrhea, stomatitis, and thrombocytopenia). In the ongoing follow-up LUNA trial, 120 patients with lung or thymus NETs will be randomly assigned to pasireotide (a long-acting somatostatin receptor analog), 10 mg everolimus daily, or the combination. In a phase II trial of the multitargeted kinase inhibitor sunitinib enrolling 41 patients with metastatic NETs (of whom 14 had foregut [lung or stomach] primary tumors), the response rate was 2%, and 83% achieved SD.[132]

Interferon alpha has demonstrated antitumor effects in advanced carcinoid, but is usually not administered until failure of somatostatin analogs because of adverse effects.[133-135] Radiolabeled somatostatin analogs remain investigational but trials have yielded encouraging initial findings.[136-139] In a phase II open-label trial, 1,109 patients with NETs (of whom 84 had bronchial carcinoid and 12 had SCLC) received 2,472 cycles of the somatostatin-based radiopeptide 90-yttrium-labeled tetraazacyclododecane-tetraacetic acid modified Tyr-octreotide ([^{90}Y-DOTA]-TOC).[136] Patients were required to have visible tumor uptake on baseline SRS. The radiographic response rate was 34%, 15% had biochemical response, and 30% had improved symptoms related to the hormonal syndrome. Notably, 9% of patients experienced permanent grade 4 to 5 renal toxicity. Tumoral uptake on baseline SRS predicted OS whereas initial kidney uptake predicted severe renal toxicity. Hepatic-directed therapies (surgery, radiofrequency ablation, arterial embolization, chemoembolization, radioembolization)[140-143] may be associated with prolonged survival if control of extrahepatic disease is achieved. Prophylactic octreotide to prevent carcinoid crisis during such procedures may be considered.

Large Cell Tumors

Historically, large cell tumors were considered to be NSCLCs that lacked diagnostic features of small cell, adenocarcinoma, or squamous cell tumors by light microscopy. With increasing use of IHC to distinguish among histologic subtypes, the proportion of cases designated large cell has decreased in recent years and currently represents fewer than 5% of NSCLCs. The large cell cancer category includes large cell neuroendocrine cancer (LCNEC). Whether LCNEC should be treated similarly to other NSCLC types or according to

small cell paradigms has been a subject of ongoing debate.[144] Although the National Comprehensive Cancer Network recommends treating LCNECs as NSCLC, some experts group and treat them as high-grade NETs together with SCLC.[145] Consistent with this approach, some SCLC clinical trials enroll cases of large cell neuroendocrine tumors. Further complicating these considerations is the nuanced and fluctuating terminology describing these diseases (Sidebar 4). Retrospective evidence supporting a SCLC-type approach to large cell neuroendocrine tumors includes the following: (1) poor prognosis, even for resected stage I tumors (33% 5-year survival)[145]; (2) improved survival with adjuvant platinum/etoposide compared to platinum with gemcitabine, vinorelbine, or paclitaxel (44 months vs. 11 months; p < 0.001)[146]; (3) substantially improved outcomes with adjuvant cisplatin/etoposide versus historic controls (5-year disease-free survival 87% vs. 35%; 5-year OS 89% vs. 47%)[147]; (4) rates of brain metastases similar to those seen in SCLC[148]; and (5) gene expression and molecular profiling indistinguishable from SCLC but clearly demarcated from other large cell tumors, lung adenocarcinoma, and well-differentiated bronchial NETs.[149-151] A proposed SCLC-based approach for large cell neuroendocrine cancers includes (1) up to 4 cycles of platinum/etoposide adjuvant chemotherapy for all resected patients, (2) chemoradiation (up to 4 courses of platinum/etoposide chemotherapy) for patients with positive nodes post-resection or unresectable stage III disease, and (3) 4 to 6 cycles of platinum/etoposide chemotherapy for stage IV disease.[145] For other cases of large cell tumors, numerous clinical trials have shown a particular benefit from pemetrexed chemotherapy, perhaps even beyond the differential effect seen in adenocarcinoma cases.[152,153]

CONCLUSION

Although most recent advances in lung cancer advances have been focused on adenocarcinoma tumors, new diagnostic and treatment approaches are emerging for squamous cell, small cell, and the rare lung cancer histologies. These developments will hopefully improve the outcomes of patients with these challenging diseases.

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Disclosures of Potential Conflicts of Interest

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LUNG CANCER

Positive Trials in Lung Cancer: Statistical versus Real Clinical Significance

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Expectations in the Care of Lung Cancer

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OVERVIEW

One of the main challenges oncologists face in the care of patients with lung cancer is the decision to incorporate new clinical trial data into routine clinical practice. Beyond the question of statistical significance, which is a more objective metric, are the results meaningful and applicable to a broader population? Furthermore, in an era of value care, do the results justify a potential increase in costs? This article discusses the main points that clinicians consider in their decision-making process and illustrates the arguments with real-life examples.

A daily challenge faced by all oncologists is how to apply the evidence from clinical trials to patients in the real world. Is a clinical trial deemed positive only on statistical or also on clinical grounds? Is the advance truly meaningful to patients, well tolerated, and affordable? Translating data into practice can be a challenge, particularly for clinical scenarios that fall outside the bounds of existing clinical practice guidelines.

In the first section of this article, we discuss trials in advanced non–small cell lung cancer (NSCLC), in which questions about statistical and clinical significance were debated among clinical experts and patient advocates. In the second section, we debate clinical trial endpoints and the applicability of results to clinical practice. In the third section, health care costs, clinical pathways, and value care are addressed.

STATISTICAL VERSUS CLINICAL SIGNIFICANCE
Definitions

When interpreting the results of a clinical trial, physicians interpret the outcomes under two different perspectives: the statistical significance and the clinical significance. The former is an objective, mathematical, and reproducible metric, whereas the latter is often undefined, largely subjective, and mostly left to the reader's judgment. Both are subject to misinterpretation. Physicians often assume that low p values are a measure of the strength of the effect (not necessarily) or that clinical significance implies that the benefit of the intervention can be applied to the entire population at risk (not necessarily). Examples abound of clinical trials that are statistically significant but clinically irrelevant or, perhaps less common, trials that did not meet statistical significance yet had clinical applicability to certain patient subsets.

Statistical significance relates to how likely the observed effect is due to random chance rather than a true difference between the treatment arms. The smaller the p value, the less likely the results were obtained by chance or that the null hypothesis was true.[1] On the other hand, there is no accepted definition of clinical significance. The closest concept is the minimally clinically important difference, which is the smallest treatment efficacy that leads to a change in a patient's management.[2] Others have attempted to define clinical significance by highlighting absolute risk reduction, as opposed to relative risk reduction, or the number needed to treat as a means to translate results of clinical trials into patient management. Quality-of-life issues and patient-reported outcomes also have been proposed as measures of clinical significance.

Chemotherapy

During the modern chemotherapy era, between the 1990s and early 2000s, when the median survival of patients with advanced NSCLC was approximately 8 months, clinical trials were designed to demonstrate a difference in median survival of approximately 2 months, arbitrarily set as a balance between a 1 month or less difference (considered not meaningful) and a 3 month or more improvement (considered very meaningful). Several of such trials, including several thousands of patients, were conducted but showed no significant differences among the various combination chemotherapy regimens.[3] One trial, which compared cisplatin/docetaxel with cisplatin/vinorelbine, raised considerable debate in its interpretation and applicability to clinical practice.[4] The difference in survival, in favor of cisplatin/docetaxel, was borderline statistically significant, but was not considered clinically significant by most clinicians. Although a commonly used combination, cisplatin/docetaxel did not gain widespread endorsement as the "regimen of choice" in advanced NSCLC.

More recently, the combination of cisplatin/pemetrexed was compared with cisplatin/gemcitabine, and a clear advantage emerged for the former in patients with nonsquamous histology.[5] This study debunked an old paradigm as the first

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to show a difference in outcome by histologic type in advanced disease. Likewise, the trials that tested the concept of maintenance have yielded solid benefits for patients and are considered both statistically and clinically significant.[6]

Monoclonal Antibodies

Two trials involving monoclonal antibodies illustrate the issues of statistical and clinical significance. The first showed that the addition of bevacizumab to chemotherapy improved survival, albeit at the cost of additional toxicity.[7] Although a similar trial in Europe did not show an overall survival advantage (despite an improvement in progression-free survival [PFS]), bevacizumab has been adopted in the United States for eligible patients. From a clinician's perspective, reluctance to add bevacizumab to chemotherapy is usually related to toxicity concerns and not so much the clinical significance of the trial. The cost-effectiveness implications are discussed below.

The second trial added cetuximab to chemotherapy in advanced NSCLC.[8] Although the study met its primary endpoint of improvement in overall survival, cetuximab was not incorporated in first-line regimens, because the difference in median survival was not felt to be clinically meaningful despite multiple subsequent attempts to refine the target patient population.

More recently, ramucirumab was combined with docetaxel in the second-line treatment of NSCLC and led to a statistically significant improvement in survival compared with docetaxel alone.[9] The magnitude of the difference in median survival was relatively small, but the results are unprecedented in the sense that no other agent, biologic or otherwise, has been shown to improve outcomes when added to a cytotoxic drug in the second-line treatment of NSCLC. It remains to be seen how these results will be interpreted by clinicians and adopted in clinical practice.

Targeted Therapy

The discovery that certain types of lung tumors harbor activating mutations that are sensitive to targeted agents has rev-

olutionized the treatment of advanced NSCLC. Trials that compared a tyrosine kinase inhibitor (TKI) with chemotherapy as first-line therapy in patients with mutated tumors (either *EGFR* or *ALK*) confirmed the benefit of the TKI approach with respect to response rate and PFS.[10] Overall survival, however, was not different, most likely because of crossover, which has led to some debate about the optimal timing and strategy of incorporating these agents in the treatment of NSCLC with sensitizing molecular alterations. In molecularly selected patients treated with the appropriate targeted agents, in comparison to standard therapies, differences in outcome tend to be robust, which illustrates that statistical significance does not always require a large number of patients when the expected treatment effect is meaningful.

ASCO Meaningful Outcomes

Members of the American Society of Clinical Oncology (ASCO) Clinical Research Committee were charged with proposing meaningful outcomes for clinical trials in several tumor types, including advanced NSCLC.[11] The primary goal was to guide the design of clinical trials that would produce meaningful outcomes for patients. In NSCLC with a nonsquamous histology, the baseline for median survival was set at 13 months, and a meaningful incremental improvement was felt to be between 3.25 and 4 months. For squamous cell cancer, the baseline was 10 months and improvement of between 2.5 to 3 months was considered meaningful. Although these goals are aspirational and assume that biomarkers will be utilized in part for the selection of patients, it raises the bar and encourages investigators, sponsors, and patients to demand more of clinical trials.

CLINICALLY MEANINGFUL TRIALS IN LUNG CANCER
Studies of Real-World Effectiveness

Given that clinical trials are conducted under highly controlled circumstances, it is reasonable to expect that trial results will not always be relevant or generalizable to one's daily practice.

Several studies in lung cancer have suggested that the outcomes now seen in clinical trials may be reflected in the general lung cancer population, but patient selection remains important. After the establishment of adjuvant chemotherapy in early-stage NSCLC as a standard, Booth et al[12] demonstrated that, although the uptake of adjuvant therapy in the target population only increased from 7% to 31%, the impact on survival was similar to the magnitude seen in clinical trials, with an increase in 4-year survival from 52.5% to 56.1% with the introduction of adjuvant therapy (p = 0.001).[12] A recent Surveillance, Epidemiology, and End Results (SEER) analysis of the real-world effectiveness of novel agents in advanced NSCLC demonstrated that the use of platinum agents, second-line docetaxel, pemetrexed, and bevacizumab all were associated with a reduced risk of death.[13] These data further support that positive results from clinical trials in advanced lung cancer do translate into benefits in clinical practice.

It is important to recall, however, that not all patients with a given diagnosis will receive the recommended treatment and

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KEY POINTS

- Although statistical significance is easier to define, clinical significance is by and large a subjective assessment and must be interpreted in the context of the clinical question addressed by the trial.
- ASCO recently proposed more aggressive outcomes for clinical trials of advanced non–small cell lung cancer, for both squamous and non-squamous histologies.
- The applicability of clinical trial data to real-life patients requires assessment of a patient's individual circumstances, which may not have been addressed in the study. This is particularly true in older patients and patients with a poor performance status.
- Clinical pathways reduce variability and decrease costs in patients with advanced non–small cell lung cancer.
- Other measures, such as a decrease in emergency department visits and prevention of hospitalization, can reduce costs while improving the quality of care.

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that multiple factors, including patient performance status, co-morbidity, organ function, patient preference, and treatment access, all factor into treatment decisions. In a real-world analysis of Canadian patients with advanced NSCLC who were treated in a single-payer public health care system, 70% of patients were assessed by an oncologist at some point, but only 26% received systemic therapy.[14] In those who received platinum doublet therapy and pemetrexed, outcomes were similar to or better than outcomes reported in clinical trials. However, older patients and those who had tumors with a squamous histology were significantly less likely to receive treatment for their disease. Similar data have been reported by Earle et al[15] from U.S. SEER Medicare data, in which 23% of patients with advanced lung cancer received systemic therapy.[15]

Thus, although oncologists are able to achieve excellent results in clinical practice, similar to those seen in trials, the achievement requires not only evidence-based practice but also careful patient selection and shared decision making.

Special Populations

Most clinical trials, from which practice guidelines are derived, include highly selected patients who have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, few or no comorbidities, and a younger age. However, given that the median age of diagnosis in lung cancer is at least age 70 and that a majority of patients have an ECOG PS of 2 or greater, how useful are clinical trial results in the patients we actually see in practice?

In a recent review of the inclusion of older adults in advanced lung cancer trials, a third of commonly cited trials specifically excluded older patients.[16] Fortunately, there are multiple trials focused on the older patient population with lung cancer,[17,18] but, again, not all patients in routine practice are suitable for the recommended therapy. Real-world analyses of older adults with lung cancer suggest that older patients do benefit from systemic therapy.[14,19] Earle et al[20] have examined the influence of age on systemic treatment for patients with advanced NSCLC in a real-world setting, using the SEER database.[20] As age increased, the likelihood of receiving chemotherapy decreased, even though patients were still referred to medical oncologists for an opinion. Treatment rates varied inversely with the number of comorbidities.

In the case of potentially curative adjuvant chemotherapy, Cuffe et al[21] demonstrated that, although older patients are prescribed adjuvant chemotherapy, the rate of uptake is approximately half of that seen in the entire population of patients with early-stage disease (16% vs. 31% overall).[21] This population-based study confirmed that a survival benefit was seen in all age groups, and the tolerability of therapy in those patients older than age 70 selected to receive treatment appeared similar to that of younger patients.

The PS presents a similar challenge, because most patients with advanced lung cancer do not present with a PS of 0 or 1. Trials have shown that platinum-based doublet therapy is superior to single-agent treatment in patients who have a PS of 2,[22-24] whereas guidelines recommend against treatment of patients who have a PS of 3.[25] This decision is more challenging in prac-

tice, in which patients who have a PS of 2 are heterogeneous[26] and there are additional factors for or against systemic therapy, including comorbidities, young age, prognostic factors, and potential delays in system access. Many databases have not routinely included PS assessment, but this is changing and will lead to more real-world data that will be available in addition to randomized trials to better inform best practices.

Evolution in Trial Design

The treatment of lung cancer has changed dramatically over the last decade. Lung cancer trials also have changed. In a recent analysis of phase III trials of systemic therapy of advanced NSCLC, there were significant shifts over a 30-year period.[27] Although overall survival was a universal endpoint 30 years ago in these studies, there has been a perceptible increase in the use of PFS as an endpoint. This may be appropriate for studies of novel agents with major clinical benefits, which require crossover for ethical reasons. However, many trials that use PFS as the primary endpoint do not meet this criterion.

The number of agents under study in lung cancer is growing,[28] as is the sample size of randomized, phase III trials—clear evidence of progress and hope in this disease. However, it appears that the magnitude of clinical benefit that investigators deem positive is falling. In the 1980s, a median survival increment of approximately 4 months in a phase III trial was considered positive, compared with 2.5 months in this last decade. The recommendations recently put forth by ASCO are described above. Though not specifically addressed, one could infer that benefit in trials for small cell carcinoma should approximate the benchmark set for squamous carcinoma. The document will not change existing trial plans nor drug approvals for lesser benefits, but it is hoped that this effort will encourage the oncology community and patients to be more demanding of the benefits gained from new therapies.

We have more agents approved in lung cancer than ever before, and decision making about treatment options has never been more complex. Patient outcomes recorded in a real-world setting, including survival and quality of life, and an open discussion about the value of therapy to the patient and society, has never been more important.

Value in Lung Cancer Care: Use of Standardized Pathways

Over the last several years, we have seen a rapid rise in the number of new agents to treat advanced NSCLC. Examples include new cytotoxic agents (e.g., nab-paclitaxel), targeted agents (e.g., erlotinib), biologic agents (e.g., bevacizumab), and, on the immediate horizon, immunomodulatory agents (e.g., nivolumab). Some of these new agents have led to only marginal advances; others have led to more impressive ones. All, however, have added substantial cost. This makes cost, as a part of decision making, more crucial today than ever before. In fact, oncologists are being asked to discuss the costs of treatment with patients, because cost of care is not simply a payer concern.[29] Most patients bear some of the cost of their cancer care in the form of copays and coinsurance, and the prescribed treatment may be unaffordable. Patients should know what lies ahead for them,

because the harshest toxicity may be financial. High costs can be devastating to patients and their families, with up to 62% of all personal bankruptcies estimated to result from medical expenses.[30]

This situation of similar outcomes among treatment regimens associated with high variations in cost sets the stage for clinical pathways. Simply put, can there be a succinct list of regimens that highlights the ones that provide the most value? And, if a pathway is implemented, can adherence to the pathway reduce costs compared with nonadherence while upholding or even improving quality and clinical outcomes? In 2005, US Oncology instituted a set of pathways, including a pathway for NSCLC. Pathway logic was embedded in the electronic medical record to ensure that pathways were visible at the point of care. The results of this program were first published in 2010.[31] This was a retrospective study looking at two groups of patients with NSCLC over the course of an 18-month period: those who were treated entirely with on-pathway regimens and those who, at any time, were treated with an off-pathway regimen. (Because pathway adherence was not expected or meant to reach 100%, there was, indeed, a large group of patients who received at least one off-pathway regimen.) Results of the study showed a 35% reduction in outpatient costs with equivalent clinical outcomes (i.e., overall survival) for patients treated on pathway. Similar results have been shown by others. Feinberg[32] reported on a payer-sponsored pathways program in which a large Mid-Atlantic payer collaborated with community oncologists in its provider network. Patients with breast, colon, or lung cancer who started chemotherapy after the initiation of the program were compared with baseline (historic) controls using the same claims database. Chemotherapy drug savings were $2,964 per patient for lung cancer.[32]

The higher the cost of cancer treatment, the more the value is challenged. A simple equation to refer to is value = outcomes/cost. If the difference in outcome is substantial between two treatments, good value may be upheld even if the superior treatment choice costs more. However, when two regimens are marginally different in outcome, higher costs quickly diminish value. Let's look at one example: the addition of bevacizumab as a third agent in the treatment of advanced, untreated NSCLC. In the pivotal ECOG study, patients were assigned to either paclitaxel/carboplatin or paclitaxel/carboplatin with the addition of bevacizumab, and bevacizumab could be continued until disease progression occurred.[7] The median survival times were 10.3 months and 12.3 months, respectively. Of note, there was a higher incidence of bleeding and treatment-related death in the bevacizumab-treated group. The costs of these regimens, using Medicare reimbursement (average sales price + 4.3%), were $625 for six cycles of paclitaxel/carboplatin and $74,000 for paclitaxel/carboplatin/bevacizumab with bevacizumab maintenance. Indeed, the results of this study were statistically significant, but were they clinically significant? Zhu et al[33] reported on 4,168 Medicare beneficiaries older than age 65 who had advanced NSCLC and compared paclitaxel/carboplatin treatment with paclitaxel/carboplatin/bevacizumab.[33] Median survival estimates were 8.9 and 9.5 months, respectively. The 1-year survival estimates were 39% for paclitaxel/carboplatin/bevacizumab and 40% for paclitaxel/carboplatin. The authors concluded that adding bevacizumab to carboplatin and paclitaxel chemotherapy was not associated with better survival among Medicare patients with advanced NSCLC.

Chemotherapy does not represent the only cost center in cancer care; in fact, it is not even the costliest piece of the total-cost-of-care pie. In a Milliman report in which $49,000 was the average annual cancer-related cost for any cancer member, $21,000 was attributed to hospital costs and $13,800, to chemotherapy ($14,000 to other categories).[34] Therefore, reducing preventable hospitalizations resulting from chemotherapy treatment is a worthwhile goal. Hoverman et al[35] showed that, when a practice implements a formal clinical pathways program and also includes an outbound nurse call system, hospitalizations and total costs can be reduced. In a program sponsored by a payer in which clinical data and claims data were shared, patients with breast, colon, and lung cancer were enrolled in this care management program over a 2-year period.[35] Compared with baseline (i.e., preprogram) practice data, there was a 48% overall reduction in emergency room visits, a 34% reduction in hospitalizations, and a 44% reduction in hospital days (i.e., length of stay). Greater adherence to clinical pathways was one of the factors contributing to these favorable results.

The simple goal of a clinical pathways initiative should be to drive value: to maintain or improve quality and control costs. To do this, pathways should be designed to favor cost-effective drugs and to challenge or exclude treatments that are of questionable clinical benefit, particularly when they are costly. This model has been shown to improve value in NSCLC. With the continued fast pace of new drugs entering the market for lung cancer, oncologists should take an active role in designing, initiating, updating, and adhering to pathways. If we do not, others will mandate it.

Disclosures of Potential Conflicts of Interest

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LUNG CANCER

Promises and Pitfalls of Lung Cancer Screening and Surveillance

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The Value of Lung Cancer CT Screening: It Is All about Implementation

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OVERVIEW

Hospitals have been gradually implementing new lung cancer CT screening programs following the release of the U.S. Preventive Services Task Force grade B recommendation to screen individuals at high risk for lung cancer. Policy makers have legitimately questioned whether adoption of CT screening in the community will reproduce the mortality benefits seen in the National Lung Screening Trial (NLST) and whether the benefits of screening will justify the potentially high costs. Although three annual CT screening exams proved cost-effective for the patient population enrolled in the NLST, uncertainty still exists about whether CT screening will be cost-effective in practice. The value of CT screening will depend largely on the strategies used to implement it. This manuscript reviews the current reimbursement policies for CT screening and explains the relationship between implementation strategies and screening value on the basis of the NLST cost-effectiveness analysis and other published data. A subsequent discussion ensues about the potential implementation inefficiencies that can negatively affect the value of CT screening (e.g., selection of low-risk individuals for screening, inappropriate follow-up visits for screening-detected lung nodules, failure to offer smoking cessation interventions, and overuse of medical resources for clinically irrelevant incidental findings) and the actions that can be taken to mitigate these inefficiencies and increase the value of screening.

In the past 5 years, lung cancer screening has evolved from a purely investigational intervention to a heavily debated topic in the U.S. public health agenda.[1,2] The debate has escalated rapidly to involve multiple stakeholders, including clinical experts, hospital leaders, medical associations, patient advocacy groups, insurance payers, and politicians.[3-7] Supporters endorse a national policy of coverage for lung cancer CT screening that is based on the following:

- The burden of lung cancer, which accounts for 27% of all cancer deaths in the United States.[8]
- The results of the NLST, a high-quality, randomized study that showed a 20% reduction in lung cancer mortality with the use of low-dose CT screening scans compared with chest radiographs.[9]
- The expectation that national implementation of CT screening will prevent more than 12,000 premature deaths per year.[10,11]
- Modeling studies claiming that CT screening is cost-effective in the commercially insured and Medicare populations.[12,13]

Screening opponents argue that the available data is premature to support broad CT screening coverage and express the following concerns:

- The NLST results may not be generalizable to a broad, high-risk population of older adults with a heavy smoking history and tobacco-related comorbidities.[2,14]

- The harms imposed by false-positive results and overdiagnoses may outweigh the benefits of screening in real-world settings.[15,16]
- Centers with lower expertise in lung cancer CT screening may not be able to reproduce the mortality benefits seen in the NLST.[17,18]
- Infrastructure gaps need to be addressed before screening implementation (e.g., consistent documentation of smoking history).[19,20]

Notwithstanding the opposing views, regulatory agencies have gradually taken a favorable position regarding the adoption of lung cancer CT screening. In December 2013, the U.S. Preventive Services Task Force (USPSTF) released a grade B recommendation to screen high-risk individuals, defined as those age 55 to 80 who have a minimum smoking history of 30 pack-years and who currently smoke or have quit within the past 15 years.[21] The Affordable Care Act requires that commercial insurance plans cover screening services that receive a grade B USPSTF recommendation, essentially guaranteeing coverage of CT screening to insured patients younger than age 65.[22] Likewise, the Centers for Medicare & Medicaid Services (CMS) has recently released a final decision to cover CT screening for Medicare beneficiaries who are age 55 to 77 and have the same minimum smoking history required by the USPSTF.[23] The USPSTF and CMS determi-

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nations indicate that insurance coverage will no longer be a barrier to screening implementation for insured individuals. New screening programs will likely proliferate across the nation, because hospitals now realize an opportunity to increase revenues by offering lung cancer CT screening and performing downstream tests and procedures prompted by a positive screening result.[24,25]

From a pragmatic standpoint, lung cancer CT screening will gradually become routine practice. Stakeholders should focus now on developing implementation strategies to ensure that lung cancer CT screening will add value to society despite the potentially high costs.[24,26,27] The next sections will discuss how implementation can influence the value of CT screening and what measures can be taken to increase the benefits of screening per dollar spent.

VALUE AND IMPLEMENTATION

Value in health care is a concept that links the benefits of a given intervention with its costs.[28] Cost-effectiveness analysis is a type of health economic evaluation that provides a value metric, usually defined as a ratio of additional costs to additional benefits of a new intervention compared with usual care (i.e., the incremental cost-effectiveness ratio or ICER).[29]

Previous cost-effectiveness analysis failed to provide conclusive evidence about the cost-effectiveness of lung cancer CT screening in the U.S. population.[12,13,26,30-34] Most of these modeling studies were poised by multiple sources of bias, because their estimates of screening effectiveness came from nonrandomized trials, and the model assumptions often were overly optimistic. Besides methodologic limitations, the analyses achieved highly variable results; some suggested that CT screening is highly cost-effective, whereas others showed that screening was prohibitively costly.

The NLST team recently published their trial-based cost-effectiveness analysis.[35] This analysis compared the costs and outcomes of three annual CT screening exams against a no-screening strategy, assuming that screening chest radiographs result in equal outcomes compared with no screening.[36] This study probably provides the most accurate

estimate of the cost-effectiveness of CT screening, given that the analysis derived estimates of effectiveness (tumor stage shift, life expectancy, and quality-adjusted life years [QALYs]) from randomized data obtained from more than 50,000 participants. Additional strengths included the availability of quality-of-life data from a sample of 12,000 participants and detailed information about health care resource utilization in patients diagnosed with lung cancer or those who had a positive screening result.

Compared with no screening, CT screening resulted in additional U.S. $52,000 per life-year gained (95% CI, $34,000 to $106,000) and $81,000 per QALY gained (95% CI, $52,000 to $186,000), respectively. Subgroup analysis suggested that CT screening is far more cost-effective when performed in individuals with higher risks for lung cancer. For example, CT screening resulted in additional $43,000 per QALY gained in current smokers compared with $615,000 per QALY gained in former smokers. Similarly, CT screening costs an additional $169,000 per QALY gained in individuals within the lowest lung cancer risk quintile compared with $52,000 per QALY gained in those within the highest risk quintile.

The NLST cost-effectiveness analysis indicates that CT screening is cost-effective under a commonly accepted willingness-to-pay threshold of U.S. $100,000 per QALY and in the context of a randomized trial.[37,38] Despite these encouraging results, some limitations of this analysis preclude a conclusion of whether CT screening will be cost-effective in practice. Sensitivity analysis showed that the cost-effectiveness estimates highly depended on the assumptions made. For example, the authors assumed that CT screening would only affect life expectancy through early detection of lung cancer. If CT screening would have other positive effects on life expectancy, perhaps through a favorable impact on smoking cessation, the ICER would be $54,000 per QALY. Conversely, CT screening would be less cost-effective ($96,000 per QALY) if the cost of managing incidental findings was $2,500 instead of $500, as assumed by the authors. In addition, the study evaluated the cost-effectiveness of only three annual CT scans, but current guidelines recommend annual CT screening for "as long as the patients are eligible," which will consist of more than three scans for most screened patients.[4,21] The impact of subsequent CT screening scans on costs and outcomes beyond 3 years remains an area of research. Another concerning point is that screening will be less cost-effective in practice if screening programs underperform in relation to NLST centers.

The conclusion, as pointed out by the authors of the NLST cost-effectiveness analysis, is that "whether screening outside the trial will be cost-effective will depend on how screening is implemented."[35] In other words, CT screening will be a valuable intervention if an infrastructure is in place to provide patients with high-quality screening services, but policy makers have questioned whether health care institutions currently have the capacity of offering these services. This concern is of upmost importance, because CT screening will be an onerous health care investment. Large-scale screening implementation is expected to cost $1.4 to $5.5 billion per

TABLE 1. Expected Costs of Lung Cancer CT Screening

Reference	Analysis Type	Perspective	Annual Average Cost per Person Screened ($)*	Annual Average Cost in Aggregate ($ in Billions)*†	Comment
Goulart et al, 2012[27]	Budget impact model	U.S. public and private payers	816	1.4 to 2.2	Target population meets NLST inclusion criteria; screening uptake of 50% to 75%
Pyenson et al, 2012[12]	Actuarial analysis	U.S. private payer	269	4.8	Target population is age 50 to 64; uptake of 50%
Roth et al, 2014[24]	Forecast model	Medicare	NR	3.5 to 5.5	Target population is Medicare beneficiaries meeting USPSTF criteria; assumed an uptake of 100% in all 5 years or an incremental uptake of 20% per year
Pyenson et al, 2014[13]	Actuarial analysis	Medicare	241	1.7	Target population is Medicare beneficiaries meeting USPSTF criteria; uptake of 50%
Cressman et al, 2014[39]‡	Prospective cohort study	Canadian public single payer	550	NR	Target population: individuals with a 3-year lung cancer risk ≥ 2%; uptake of 100% (first scan) and 85% (second scan)

Abbreviations: NLST, National Lung Screening Trial; NR, not reported; USPSTF, U.S. Preventive Services Task Force.
*Costs are inflated to 2014 U.S. dollars.
†Costs reflect total expenditures in the entire target population from the respective healthcare system perspective.
‡Costs were converted to U.S. dollars by applying a conversion factor of 0.8028.[66]

year to public and commercial health care payers, mainly depending on how many individuals will undergo screening (Table 1).[12,13,24,27,39] The number of patients screened will depend at least in part on patient's beliefs about lung cancer screening. Fear of lung cancer may motivate patients to pursue screening, while concerns for out-of-pocket costs, anxiety about CT scan results, and fear of radiation exposure may represent barriers to screening.[40] Besides the economic impact, screening will result in additional diagnostic imaging tests and procedures for lung nodules and incidental findings.

A careful implementation plan should include not only efficient management of screening-detected lung nodules but also the development of processes and delivery of smoking cessation interventions. The next section describes areas of potential implementation inefficiencies based on available data, how they can negatively affect the value of CT screening, and potential actions to mitigate these inefficiencies.

IMPLEMENTING LUNG CANCER CT SCREENING: POTENTIAL AREAS OF INEFFICIENCY

Implementation of lung cancer CT screening will require broad infrastructural developments, including building capacity with additional CT scanners and radiology staff and developing structured radiology reports.[18] A description of all necessary implementation processes is out of the scope of this manuscript. The goal of this section is to highlight the processes that are expected to influence the value of CT screening in practice. These include the selection of high-risk screening candidates, follow-up for positive screening results, provision of smoking cessation interventions, and management of screening incidental findings.

Selection of High-Risk Screening Candidates

The NLST cost-effectiveness analysis provides compelling evidence that the value of CT screening decreases substan-

tially when screening is performed in a lower-risk population, including individuals who met the NLST inclusion criteria. This negative impact on value occurs because many more additional scans need to be performed to detect one early-stage lung cancer in lower-risk screenees. The costs of CT screening will become prohibitive if new programs routinely screen individuals irrespective of their lung cancer risk (e.g., light or never smokers), potentially reaching $19 billion per year, and such practice should be strongly discouraged.[41]

The value of any screening program, and CT screening in particular, also depends on identifying and offering this intervention to high-risk individuals. Failure to offer screening to all eligible individuals will decrease the effectiveness and value of screening in any given health care system.[19]

Early evidence suggests that new screening programs are performing CT screening in lower-risk patients while at the same time potentially missing the opportunity to screen high-risk individuals (Table 2). Unawareness by primary care providers (PCPs) of the role of CT screening is one of the main reasons for inefficient selection of screening candidates. A recent survey of 212 PCPs from an academic medical center showed that only 12% of them had ordered CT screening in the prior year; 52% knew fewer than three of six guideline components of CT screening, and 24% did not know any screening guidelines.[42] Of 89 patients included in our single-center screening registry, 19 (21%) did not meet any eligibility criteria for screening; PCPs were the referral source for the majority of these ineligible individuals.[43]

Physician education should take priority in the early phases of screening implementation, because PCPs are the major source of screening referrals.[44,45] The Lahey clinic received more than 500 referrals of eligible high-risk candidates within 1 year of launching a CT screening program after conducting extensive PCP-oriented educational campaigns.[46] Most other screening programs have had lower referral num-

TABLE 2. Potential Inefficiencies That May Decrease the Value of Lung Cancer CT Screening and Potential Solutions

Screening-Related Process	Potential Inefficiency	Negative Impact on Value	Potential Solution(s)
Selection of Eligible Individuals	High-risk individuals not being screened:	↓ Screening effectiveness	• Physician educational campaigns
	• PCP's inaccurate knowledge about screening		• Patient counseling
	• Patients' views against screening		• Use of EHRs to document smoking history
	• Inconsistent documentation of smoking history in medical charts		• Use of EHR-based physician reminders
	Low-risk individuals being screened:	↓ Screening effectiveness; ↑ costs	• Patient counseling
	• Worried-well patients demanding screening		• Physician educational campaigns
	• PCP's inaccurate knowledge about screening		• Restriction of insurance coverage to high-risk individuals
Follow-up of Positive Screening Results	Lower expertise in the management of lung nodules	↑ Costs; ↓ screening effectiveness	• Adherence to guidelines
	• Overuse of diagnostic tests for false-positive results		• Multidisciplinary management
	• Delayed lung cancer diagnosis		• Referral to high-expertise center
Smoking Cessation	PCP's lack of time for counseling	↓ Screening effectiveness	• Inclusion of smoking cessation specialists in the screening program workforce
	• Current smokers continuing to smoke		
	• Former smokers going back to smoke		
Management of Incidental Findings	Overuse of resources for clinically irrelevant findings	↑ Costs	• Structured radiology report with follow-up recommendations
	• Defensive medicine		• Physician education
	• Patient anxiety		
	Overlook clinically relevant, incidental findings	↓ Screening effectiveness	

Abbreviations: PCP, primary care physician; EHR, electronic health record.

bers, mostly because of PCP unawareness and lack of insurance coverage for screening.[43,47,48]

Many low-risk individuals may demand to undergo CT screening because of a fear of developing lung cancer, despite being ineligible for screening (i.e., worried well patients).[20] Some of these patients will self-refer to a screening program, whereas others will request a referral from their PCPs who, in many cases, will order screening to honor the patient's request. Media campaigns usually target high-risk individuals, but an unintended consequence of these campaigns is that low-risk individuals feel that they need to pursue screening.

Screening programs should offer evidence-based counseling to all patients undergoing screening, particularly those who are at low risk and are ineligible by guidelines criteria.[20,21] A balanced discussion about the benefits and harms of screening based on patient's risk may ensure that screening is performed preferably in high-risk individuals. Decision-aid and risk-prediction tools may be particularly useful to inform patients about their individual risk of developing lung cancer and whether screening is more likely to be beneficial or harmful.[49] Although validated decision aids for CT screening are not available routinely, clinical trials currently are testing the effectiveness of these tools in counseling individuals.[50] To incentivize physicians to counsel patients, health insurance plans should create payment fees for CT screening counseling visits. In fact,

CMS requires documentation of a counseling visit to reimburse claims for CT screening.[23]

No evidence exists to inform whether counseling should be provided by PCPs or by screening experts. Until PCPs become more familiar with screening guidelines, the burden of counseling patients should fall on clinical experts working for screening programs (e.g., pulmonologists).[51]

At present, most clinics do not use a systematic approach to identify high-risk individuals; PCPs may order screening when they have information about smoking history and are aware of the indications for CT screening. This opportunistic approach seems unlikely to capture a large fraction of eligible screening candidates. Detailed smoking history often is not available or is not consistently reported in medical records; even when this information is available, a busy clinician may not have the time to counsel patients about screening.[19]

A potentially effective strategy to identify high-risk patients is to require that clinical staff record the elements of smoking history necessary to determine screening eligibility in electronic health records (EHRs). This process can be used to generate electronic reports that screening programs can use to contact eligible patients and offer screening. Evidence suggests that this strategy effectively captures high volumes of eligible screening candidates. The screening program at the City of Hope Medical Center implemented a similar process, in which clinical staff enters smoking history in EHRs

every 6 months in primary care clinics. In the 3 months before implementing this strategy, the program identified and screened four patients. In the 7 subsequent months, the program screened 58 eligible patients.[48]

Follow-up for Screening-Positive Results

Most positive screening results will consist of solid and non-solid lung nodules; the vast majority of these nodules will not be lung cancer and will constitute false-positive results.[9] An efficient work-up of lung nodules is crucial to maximize screening effectiveness through expedited diagnosis of lung cancer while minimizing the harms and costs of unnecessary tests and procedures for false-positive results (Table 2).

The American College of Radiology (ACR) and the National Comprehensive Cancer Network (NCCN) have developed guidelines for work-up of patients with screening-detected lung nodules.[4,52] The ACR guidelines provide a classification of lung nodules according to their risk of being lung cancer and respective recommendations for follow-up visits (Lung-RADS).[53] The NCCN guidelines represent an amalgamation of previously published guidelines for the management of incidentally detected lung nodules and expert consensus.[54] Although no formal evidence shows that these guidelines result in cost-effective management of screening-detected lung nodules, their recommendations provide a reasonable framework on which new screening programs can base their work-up algorithms until further research informs about the most cost-effective diagnostic strategies.

Because screening programs are just becoming operational, no real-world data are available to inform adherence to guideline recommendations for the work up of screening-detected nodules. Likewise, very little data exists to inform how the work up for lung nodules in practice compares with the diagnostic resources utilized in large trials such as the NLST.[47] Screening registries will play a critical role in informing adherence to guidelines as screening is implemented. Until more data from registries become available, new screening programs are encouraged to strictly follow the recommendations from current guidelines.

The management of screening-detected nodules is a potentially complex process that in most cases requires follow-up visits with additional low-dose CT scans over multiple points in time and occasionally requires invasive procedures.[16,18,20] Appropriate follow-up care requires the involvement of a multidisciplinary team of experts in lung cancer screening, including radiologists, pulmonologists, thoracic surgeons, and oncologists.[55] Excessive and often unnecessary use of diagnostic resources can occur when a multidisciplinary team is not available to guide the investigation of screening-detected lung nodules, resulting in increased costs and delays in the diagnosis of lung cancer. Clinics without this level of expertise should refer their patients to centers that can offer an integrated and multidisciplinary diagnostic approach to screening-detected lung nodules and expedited treatment for screening-detected lung cancers.[41]

As CT screening becomes routine practice, clinics can expect larger numbers of patients with early-stage lung cancer.

This may represent an opportunity for comparative-effectiveness studies of treatment modalities that potentially involve less morbidity than lobectomies, including minimally invasive surgery and stereotactic radiation techniques.[56] The role of these alternative treatments in screening-detected lung cancers remains an area of investigation; clinical trials and cost-effectiveness analyses of these approaches should receive priority as strategies offering high potential to increase the value of CT screening.

Provision of Smoking Cessation Interventions

Smoking cessation is a topic that has simultaneously incited consensus and controversies in the lung cancer CT screening debate. The consensus is that CT screening does not replace the role of smoking cessation interventions for current smokers. The main controversy surrounds the impact of CT screening on smoking behavior: some postulate that CT screening serves as a teachable moment to encourage smoking cessation, leading smokers to quit; others worry that a normal screening result provides false reassurance that smoking is safe, encouraging current smokers to continue smoking or former smokers to restart smoking.[4] Recent evidence supports the former claim, whereas no evidence confirms or contests the latter.

A subsequent analysis of the NLST showed that approximately 40% of individuals who were actively smoking at trial enrollment had quit at 7 years of follow-up and that the likelihood of quitting increased with the degree of abnormality detected by screening.[57] This quit rate is considerably higher than the 5% rate reported in the general population of adult smokers.[58,59] The analysis does not answer the question of whether this high quit rate resulted from higher motivation to quit or from higher adherence to smoking cessation interventions. Regardless, the NLST results do support the notion that positive screening results encourage smokers to quit, possibly because of fear of developing lung cancer.

Additional research is necessary to inform whether current smokers are receiving smoking cessation interventions at the time of screening. The impact of screening on smoking behavior among former smokers is also an area of investigation. These data can better inform how to engage screening with smoking cessation programs in real practice.

Meanwhile, every effort should be made to help current smokers quit. Cost-effectiveness analyses suggest that CT screening is more cost-effective if quit rates double after screening and when current smokers receive counseling and pharmacologic smoking cessation interventions.[26,34] The value of CT screening will depend, at least in part, on implementing successful smoking cessation practices.

Realistically, PCPs do not have enough time to provide comprehensive smoking cessation. Like CT screening, smoking cessation is a process that may involve multiple interactions with patients; smokers often undergo several quit attempts before achieving durable smoking cessation. To ensure appropriate longitudinal guidance on smoking cessation, screening programs should include smoking cessation specialists in their workforce (Table 2).

Less costly interventions may successfully help smokers quit and may add value to CT screening. These include the use of telephone quit lines and web-based smoking cessation resources.[60,61] Additional modeling studies should evaluate the cost-effectiveness of these interventions against traditional one-to-one or group counseling sections and pharmacologic interventions, respectively.

Management of Screening Incidental Findings

Incidental findings consist of screening abnormalities other than those suspicious for lung cancer (e.g., coronary calcifications, emphysema). The impact of these findings on the value of CT screening is unclear. The NLST cost-effectiveness analysis suggests that the value of CT screening decreases as the costs of managing incidental findings increase, but these costs were based on assumptions rather than observed costs.[35] At least in theory, the management of incidental findings can either increase or decrease the value of CT screening (Table 2). Appropriate handling of clinically relevant incidental findings may increase screening effectiveness and value[62]; work up and treatment of clinically irrelevant findings may increase costs and decrease value, respectively.

Data from the NELSON trial and NLST suggest a low prevalence of clinically relevant incidental findings (8% and 10%, respectively).[63,64] The Lahey CT screening program has reported a similar low prevalence of clinically relevant findings.[65] In practice, relevant and irrelevant incidental findings are reported frequently enough to trigger further use of medical resources in a large proportion of patients, without a clear benefit. The pan-Canadian early detection of lung cancer study revealed emphysematous changes in 1,195 patients (58%) who underwent a first CT screening exam; our registry study at the Seattle Cancer Care Alliance showed a 73% prevalence of incidental findings in the first CT screen.[39,43] Clearly, additional research is needed to determine the impact of incidental findings on the value of CT

screening. Screening registries represent an excellent research platform to address this question.

Patient anxiety and defensive medicine also can increase screening costs and decrease value. Patients may feel anxious when informed about the presence of incidental findings on screening and may request additional work up. Physicians may order unnecessary and costly evaluations for incidental findings out of concern about malpractice claims. Screening program leaders should be aware of the unintended consequences of reporting incidental findings and should develop careful language in screening reports that specifies recommendations for follow-up visits, including a statement that no further evaluations are necessary for clinically irrelevant findings. Specific recommendations, including those for no follow-up care, will provide physicians and patients with the reassurance that additional work up can be deferred safely, thus avoiding an escalation of costs.

FINAL CONSIDERATIONS

Lung cancer CT screening may save thousands of lives and add value to society if implemented in a manner that reproduces the mortality benefits seen in the NLST while minimizing harms and costs.

Screening programs should implement practices that will likely increase the value of CT screening, including counseling and selecting high-risk patients for screening, monitoring adherence to guidelines for screening-detected lung nodules, offering smoking cessation interventions, and making specific recommendations for follow-up of screening incidental findings.

Finally, value is only one angle to consider when implementing CT screening. Policy makers and clinicians also need to take into account sociodemographic disparities and other issues that can prevent equitable access to screening. Only by taking a comprehensive approach will we achieve the promise of CT screening: decrease the huge burden imposed by lung cancer.

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LUNG CANCER

Updates in the Multimodality Management of Stage III Lung Cancer

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The Latest in Surgical Management of Stage IIIA Non–Small Cell Lung Cancer: Video-Assisted Thoracic Surgery and Tumor Molecular Profiling

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OVERVIEW

Stage IIIA non–small cell lung cancer (NSCLC) remains a treatment challenge and requires a multidisciplinary care team to optimize survival outcomes. Thoracic surgeons play an important role in selecting operative candidates and assisting with pathologic mediastinal staging via cervical mediastinoscopy, endobronchial ultrasound, or esophageal ultrasound with fine needle aspiration. The majority of patients with stage IIIA disease will receive induction therapy followed by repeat staging before undergoing lobectomy or pneumonectomy; occasionally, a patient with an incidentally found, single-station microscopic IIIA tumor will undergo resection as the primary initial therapy. Multiple large clinical trials, including SWOG-8805, EORTC-8941, INT-0139, and ANITA, have shown 5-year overall survival rates of up to 30% to 40% using triple-modality treatments, and the best outcomes repeatedly are seen among patients who respond to induction treatment or who have tumors amenable to lobectomy instead of pneumonectomy. The need for a pneumonectomy is not a reason to deny patients an operation, because current operative mortality and morbidity rates are acceptably low at 5% and 30%, respectively. In select patients with stage IIIA disease, video-assisted thoracic surgery and open resections have been shown to have comparable rates of local recurrence and long-term survival. New developments in genetic profiling and personalized medicine are exciting areas of research, and early data suggest that molecular profiling of stage IIIA NSCLC tumors can accurately stratify patients by risk within this stage and predict survival outcomes. Future advances in treating stage IIIA disease will involve developing better systemic therapies and customizing treatment plans on the basis of an individual tumor's genetic profile.

Stage IIIA non–small cell lung cancer (NSCLC) encompasses a heterogeneous group of tumors with a wide range of sizes, degrees of local invasion, and mediastinal lymph node involvement. The variety of presentation within this stage poses an ongoing challenge to thoracic oncologists to make evidence-based treatment recommendations and accurately predict outcomes in different subgroups of patients. The features that define stage IIIA presentation suggest imminent systemic disease, and 5-year overall survival outcomes remain poor at only 24% for stage IIIA tumors and 9% for stage IIIB tumors.[1] However, certain patient populations, particularly those whose tumors are downstaged by induction therapy and those who undergo lobectomy, have decent outcomes with the appropriate multimodality regimens. Thoracic surgeons play an important role as part of an interdisciplinary care team in selecting operative candidates with stage IIIA disease for whom definitive local control offers the best chance of long-term survival.

ROLE OF THORACIC SURGEON IN PROPER STAGING AND PATIENT SELECTION

Accurate clinical staging in patients with newly diagnosed NSCLC is important to optimize the benefits from surgery and to avoid attempting curative resections in the setting of systemic disease. After a complete staging work-up that includes a PET/CT and brain MRI, staging for patients with locally advanced, stage IIIA, and select T4 disease should be discussed by a multidisciplinary care team that includes a thoracic surgeon. Initiating thoracic surgeon involvement at the time of diagnosis is particularly important in stage IIIA NSCLC, because surgeons play a critical role in determining which patients are surgical candidates and in planning mediastinal biopsies during initial staging and restaging.

Nearly half of all patients will have mediastinal disease at the time of diagnosis; therefore, any mediastinal lymph nodes suspicious for metastatic disease on PET/CT require pathologic confirmation. Cervical mediastinoscopy remains the gold-standard approach to pathologically stage the mediastinum, but other methods—including endobronchial ultrasound (EBUS) and esophageal ultrasound (EUS) with fine needle aspiration (FNA)— have the benefit of being easily repeated if restaging is necessary. This is an important consideration in stage IIIA disease; many of these patients will require pathologic mediastinal staging at the time of diagnosis and again after induction treatment before a surgical re-

section, because imaging-based mediastinal restaging after treatment is unreliable.

PET/CT for initial staging of the mediastinum has a reported sensitivity of 80% and a specificity of 70%.[2] However, it is much less accurate for restaging after chemotherapy or radiation. A meta-analysis of the accuracy of PET mediastinal restaging after neoadjuvant treatment demonstrated an overall sensitivity of 64% and a specificity of 85% in assessing mediastinal disease.[3] Given these inaccuracies, pathologic restaging with a repeat cervical mediastinoscopy or an EBUS/EUS-FNA is recommended before proceeding with surgery. Despite these recommendations, a 2010 survey of National Comprehensive Cancer Network (NCCN) member institution practice patterns showed that 60% do not pathologically restage the mediastinum after neoadjuvant therapy to make a final decision regarding surgery.[4]

For mediastinal staging, cervical mediastinoscopy remains the gold standard, with a sensitivity of 86% and a negative predicted value of 95% for detecting metastatic disease.[5] Large studies of initial mediastinoscopy have shown it to be safe, with a 0.05% procedure-related mortality rate and a 0.6% complication rate that mostly is due to vocal cord dysfunction and arrhythmia.[5,6] However, repeating a cervical mediastinoscopy is technically challenging, more dangerous, and less accurate. Fibrosis and scarring from the first attempt obliterates natural tissue planes, and interval radiation further worsens this process. For this reason, we recommend saving the first mediastinoscopy for restaging just before surgery and using EBUS and EUS-FNA during the initial staging work-up.

In situations where is it absolutely necessary, repeat mediastinoscopy is possible, and experienced institutions have

published outcomes demonstrating its safety. Marra et al[7] reported repeat mediastinoscopy in 104 patients with lung cancer after induction chemoradiotherapy. Repeat mediastinoscopy was possible in 98% of patients, with 0% mortality and 1.9% morbidity as a result of left recurrent nerve palsy. Repeat mediastinoscopy had a sensitivity of 61%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 85%. Successful biopsy results are dependent on the lymph node station; the best results are seen for stations 2R, 4R, 4L, and 7, with successful biopsy rates of 88% to 98% at first mediastinoscopy and 63% to 84% at repeat mediastinoscopy. Station 2L, which must be approached with caution because of its proximity to the left recurrent laryngeal nerve, was successfully biopsied during only 56% of first mediastinoscopies and 21% of repeat procedures.[7] Call et al[8] during a similar experience with 101 repeat mediastinoscopies reported a sensitivity of 74%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 79%.[8] These data show that repeat mediastinoscopy is feasible; however, individual surgeon experience and comfort level are of paramount importance before attempting a repeat mediastinoscopy.

EBUS- and EUS-FNA are useful and accurate alternatives for staging the mediastinum. EBUS-FNA has a reported sensitivity of 92%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 97% for staging mediastinal lymph nodes in NSCLC.[2] EUS-FNA is an additional technique that was first developed to stage gastric and esophageal cancer but that has gained popularity in lung cancer as well, because it provides access to the posterior mediastinum through the esophageal wall. A meta-analysis demonstrated an overall sensitivity of 83% and a specificity of 97% of EUS-FNA at detecting malignant lymph nodes in patients with NSCLC.[9] After induction treatment, Annema et al[10] reported their experience with 19 consecutive patients who had NSCLC with mediastinal disease who required restaging. Biopsy specimens were successfully obtained via EUS-FNA from at least one lymph node station in 89% of patients and from two different lymph node stations in 47% of patients.[10] Both EBUS and EUS can be performed safely and accurately after induction treatment for restaging purposes. At our institution, we preferentially use EBUS and EUS-FNA for initial mediastinal staging and reserve the first attempt at mediastinoscopy for restaging before surgery.

Patient selection for surgery in stage IIIA disease depends on the surgeon's experience and the patient's ability to tolerate a pulmonary resection. At our institution, we strongly believe in the benefits of definitive local control and have an aggressive surgical approach. We offer resection to patients who have stage IIIA tumors despite size, invasion into the main bronchus, mediastinal pleura, parietal pericardium, or resectable N2 disease as long as a complete R0 resection with clean margins is achievable. We also offer resection to select patients with T4 disease on the basis of the presence of isolated but resectable tumor nodules in a different ipsilateral lobe and tumors invading mediastinal structures, vena cava,

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KEY POINTS

- Thoracic surgeons should be involved early in the multidisciplinary management of stage IIIA disease in patients to identify operative candidates and help guide pathologic staging of the mediastinum.
- A triple-modality treatment approach in patients with N2 mediastinal disease can achieve 5-year overall survival rates of up to 30% to 40%; good prognostic indicators are a response to induction treatment and the need for lobectomy instead of pneumonectomy.
- Pneumonectomy outcomes have improved over time, and the need for a pneumonectomy is not a reason to avoid a surgical resection in patients who can tolerate the procedure.
- Video-assisted thoracic surgery survival outcomes are comparable to those after open thoracotomy, though no randomized trials have directly compared the two approaches in stage IIIA disease.
- In the era of personalized medicine, genetic profiling of stage IIIA tumors for prognostic risk stratification is a promising area of new research that could help guide treatment decisions and better predict patient-specific outcomes within this heterogeneous stage.

atrium, or diaphragm when we believe we can perform an R0 resection. Patients with extensive T4 tumors in whom a complete resection is unlikely are generally poor surgical candidates. All of these treatment decisions are made as part of a multidisciplinary care team discussion and with the agreement of our thoracic oncologists and radiation oncologists.

MANAGEMENT OF STAGE IIIA WITH N2 MEDIASTINAL INVOLVEMENT

Patients with stage IIIA disease and N2 lymph node involvement range from those with small tumor foci in a central node to those with bulky multi-station disease who, therefore, pose the greatest treatment challenge for thoracic oncologists. The nature of mediastinal disease portends bad outcomes and possible microscopically systemic, stage IV disease. However within this group, surgery can provide definitive local control and lead to long-term survival for some patients. Randomized, controlled trials to evaluate the value of surgery in N2 disease have been continually plagued by enrollment difficulties and many have closed prematurely. In addition, they have been affected over time by changes in staging criteria, evolving induction chemotherapy and radiation trends, and the development of novel chemotherapy agents.

Early clinical trials, such as the Southwest Oncology Group (SWOG) 8805 study, demonstrated that patients with initially unresectable NSCLC could have their tumors downstaged with induction chemoradiation and ultimately undergo successful surgical resection. In this trial, patients whose tumors did not respond to induction treatment or had positive margins or nodes in the surgical specimen were given additional chemotherapy and radiation. Patients who underwent surgery had a median overall survival of 23.6 months versus 22.2 months among patients who only received chemotherapy and radiation. The 3-year overall survival with triple-modality treatment was 27% versus 20% in the chemotherapy and radiation group, respectively. Patients whose tumors were downstaged to N0 disease after induction chemoradiation had the best outcomes, with triple-modality treatment with a 3-year survival rate of 44%. Collectively, these outcomes demonstrated that a triple-modality treatment approach was not worse than chemotherapy and radiation alone and, in certain subgroups of patients, led to improved survival outcomes.

More recently, two large, randomized clinical trials have examined the benefits of surgery in patients with stage IIIA, N2 NSCLC: the European Organization for Research and Treatment of Cancer (EORTC) 8941 trial and the North American Intergroup (INT) 0139 trial. EORTC 8941 compared surgery and radiation therapy in patients with stage IIIA N2 disease who responded to induction chemotherapy. Of 579 enrolled patients, 61% responded to three cycles of platinum-based induction chemotherapy and, therefore,

were randomly assigned to either radiotherapy or surgery. A complete surgical resection was achieved in 50% of patients randomly assigned to surgery. Pneumonectomy was required in 47% of patients, and the overall operative mortality rate was 4%. Adjuvant radiotherapy was given to 40% of patients after surgery. There were no differences in survival between patients who underwent a surgical resection or radiotherapy, with a median survival of 16.4 months versus 17.5 months, respectively, and a 5-year overall survival rate of 15.7% and 14.0%, respectively.[12] This trial has been criticized for inadequate clinical staging, without PET/CT or brain MRI, which likely led to the inclusion of some patients with later-stage IIIB and IV disease. In addition, the study reported a relatively low rate of a complete R0 surgical resection and a high rate of pneumonectomy, which may reflect the advanced disease in these patients and account for the greater morbidity in the surgical arm of the study.[4]

As data emerged that concurrent neoadjuvant chemotherapy and radiation yielded better outcomes than sequential administration, new randomized, controlled trials were designed to define the role of surgical resections. INT 0139 involved 429 patients with pathologically proven stage IIIA N2 disease who were first treated with induction chemotherapy plus radiation and then randomly assigned to surgery followed by adjuvant chemotherapy or continued radiation, up to 61 Gy, followed by more chemotherapy. A complete surgical resection was achieved in 71% of patients randomly assigned to surgery. Overall there were no differences between patients who underwent a complete surgical resection versus definitive, full-dose radiation, with median overall survival times of 23.6 months versus 22.2 months, respectively, and 5-year survival rates of 27% and 20%, respectively. However, PFS was significantly improved with surgery (12.8 months vs. 10.5 months; p = 0.017). Survival outcomes also were significantly better in the subgroup of patients whose tumors were downstaged to N0 by induction chemotherapy, with a median overall survival time of 34.4 months and a 5-year survival rate of 41% (p = 0.0001).[13]

Another large trial to include patients with stage IIIA disease was the Adjuvant Navelbine International Trialist Association (ANITA) trial, which demonstrated a survival benefit with adjuvant chemotherapy in patients who had stage IB to IIIA, fully resected lung cancer. Among patients who received adjuvant cisplatin-based chemotherapy and radiation after surgery, there was a 5-year overall survival rate of 47% among patients with N2 disease.[14] Similar outcomes have been reported in single-institution, retrospective studies of tri-modal therapy in patients with stage IIIA N2 disease. Askoxylakis et al[15] reported a median survival time of 32 months and 1-, 3-, and 5-year survival rates of 85%, 50%, and 36%, respectively; 32% of patients who underwent an R0 resection remained disease free at 5 years.[15]

These clinical trials have consistently shown that certain characteristics are good prognostic indicators in stage IIIA N2 disease. A response to treatment or downstaging of the

mediastinum is predictive of more favorable outcomes after tri-modality treatment. Patients who undergo lobectomy have better overall survival times than patients who require bi-lobectomy or pneumonectomy, which may be related to both operative mortality and more advanced disease among the pneumonectomy group. Also, patients who have tumors with squamous cell histology have an overall better prognosis than those who have adenocarcinoma; one study reported a 43% 5-year overall survival rate for squamous cell histology compared with 36% for adenocarcinoma.[11,15,16] Tri-modal therapy offers the best chance of definitive local control and long-term survival for these patients with stage IIIA disease, and we recommend an aggressive approach in considering a patient for a potentially curative surgical resection.

At our institution, we typically relegate patients who have bulky N2 disease to induction chemotherapy or chemoradiation. If these patients have tumors that are downstaged on repeat imaging, and if we feel that all the node disease can be encompassed with a radical mediastinal lymphadenectomy, then we proceed with a surgical resection at that time. The default operation at our institution is a radical mediastinal node dissection, and we are aggressive in offering resection for patients with N2 disease, because we believe we can clear all of their disease. Patients who have bulky N2 disease with tumors that are not downstaged by induction therapy will continue on to definitive chemoradiation.

PNEUMONECTOMY: WORTH THE MORBIDITY AND RISK?

In the past, published outcomes after pneumonectomy were poor and often cited as reasons to avoid surgery, because the mortality from the operation itself was so high that it offset any potential survival benefits. INT 0139 trial data showed that patients with stage IIIA N2 disease who underwent pneumonectomy after induction chemoradiation had a 27% mortality rate because of postoperative complications of pneumonectomy, mainly acute respiratory distress syndrome and other respiratory causes. Performing a pneumonectomy did not improve survival outcomes, with 5-year survival rates of 22% and 36% in patients who underwent pneumonectomy and lobectomy, respectively.[13] The high perioperative mortality rate likely undercut any long-term survival benefits seen in those patients.

In addition to procedure-related mortality, retrospective studies have shown that the need for a pneumonectomy, compared with a lobectomy, is a poor prognostic indicator. Steger et al[17] reported survival outcomes with tri-modal therapy in 146 patients with stage IIIA NSCLC, 53% of whom required pneumonectomy after induction chemotherapy and radiation. Overall, approximately half of the patients experienced treatment-related comorbidity regardless of lobectomy or pneumonectomy, and the 30-day mortality was 2.7% as a result of four deaths in patients who underwent a pneumonectomy. Though none of the differences were statisti-

cally significant, the 5-year overall survival rate was 45% versus 33%, and the median survival was 55 months versus 26 months, in patients who underwent lobectomy or bi-lobectomy versus pneumonectomy, respectively. The need for a left-sided pneumonectomy was a favorable prognostic indicator, with a 5-year survival rate of 36% versus 29% in patients who underwent a right-side pneumonectomy.[17]

More recent studies from experienced and high-volume institutions have reported increasingly favorable outcomes, citing procedure-related mortality rates of less than 5% and 5-year survival rates ranging from 30% to 38% in patients with stage IIIA disease who have undergone a pneumonectomy as part of a multimodality treatment regimen.[17,18] A recent, retrospective review of 36 consecutive patients at a single institution who underwent pneumonectomy for stage IIIA lung cancer found encouraging 1-, 3-, and 5-year survival rates of 66%, 38%, and 38%, respectively. The 5-year survival rate for patients who underwent adjuvant therapy was 60% compared with only 33% in patients who received only neoadjuvant therapy and 30% in patients treated with surgery alone.[18]

In experienced centers, pneumonectomy can be safely performed as a curative resection with low operative mortality and acceptable morbidity. Contemporary pneumonectomy outcomes data from the Society for Thoracic Surgeons (STS) General Thoracic Surgery Database (GTSD) has shown a mortality rate of 5.6% and a 30.4% rate of major perioperative adverse events for all patients undergoing pneumonectomy. Analysis of the GTSD has revealed that age older than 65, male sex, congestive heart failure, forced expiratory volume in 1 second less than 60% of predicted, and receipt of neoadjuvant chemoradiotherapy are all predictors of postoperative complications.[19]

At our institution, we have developed several perioperative protocols to decrease complications and mortality from pneumonectomy. During anesthesia induction, patients receive 120 milligrams of intravenous methylprednisolone to decrease the cytokine storm and blunt the inflammatory response from a pneumonectomy. Throughout the operation, anesthesiologists aim to maintain tight volume control with sparing use of fluids, to avoid blood product transfusions, and to use acute respiratory distress syndrome (ARDS) ventilator setting that include low tidal volumes, low fraction of inspired oxygen, and minimal peak pressures. All immediate postoperative care of patients after pneumonectomy occurs in a cardiac intensive care unit with specialized intensivists, nurses, and respiratory therapists. These coordinated efforts of our experienced team have led to low post-pneumonectomy morbidity and mortality.

In experienced centers, pneumonectomy can be performed with acceptably low operative mortality and good long-term survival as part of a tri-modal treatment regimen; therefore, the need to perform a pneumonectomy is not a reason to deny patients the opportunity for definitive local control. Unfortunately, the need for a pneumonectomy also portends more advanced disease, and these patients have shorter sur-

vival times than those who can be treated with lobectomy alone.

WHEN IS VIDEO-ASSISTED THORACIC SURGERY APPROPRIATE?

There is increasing data to show that larger pulmonary resections can be safely performed with a minimally invasive video-assisted thoracic surgery (VATS) technique and that VATS is acceptable for stage IIIA disease. Initially, many characteristics that defined stage IIIA tumors—including larger tumor size, involvement of adjacent structures, any nodal involvement, centrally located tumors, and previous chemotherapy or radiation—were considered relative contradictions for VATS. However, increasing VATS experience demonstrates that even tumors with these features can be safely resected with a VATS approach.[20]

There is also concern that complete oncologic mediastinal lymph node dissections with VATS are more difficult to perform and, therefore, that patients may receive inferior oncologic resections. Merritt et al[21] performed a retrospective review of lymph nodes sampled during VATS versus open lobectomies for clinical N0 disease. They found significant differences in the mean number of lymph nodes sampled (15 nodes in open vs. 10 in VATS; p = 0.003) and in the percentage of patients whose tumors were upstaged to pathologic N1 or N2 status (25% after open vs. 10% after VATS; p = 0.05). The difference in pathologic upstaging would lead to important differences in postoperative treatment and, potentially, long-term survival outcomes for these patients.[21] Conversely, others have shown no differences in the number of total or mediastinal lymph nodes sampled and no differences in disease-free survival or 5-year overall survival rates between the two approaches.[22]

Multiple nonrandomized studies have retrospectively examined long-term survival after VATS compared with open thoracotomy and shown no survival detriment with VATS in stage IIIA disease. To examine VATS lobectomy, Yang et al[23] compared outcomes in a total of 621 patients. Of these, 67 patients has stage IIIA or greater NSCLC, and a VATS lobectomy was feasible in 13% of those patients with later-stage disease. In patients with stage IIIA disease who were undergoing VATS lobectomy, Yang et al observed a 5-year overall survival rate of 22% that was not different from the 24% 5-year overall survival rate for patients who underwent open thoracotomy.[23] However, the study was not randomized, so the patients selected by the surgeons for VATS lobectomy likely had smaller disease burdens and, therefore, more favorable prognoses.

Pneumonectomy in patients with stage IIIA disease also can be performed via VATS. Battoo et al[24] recently published a report of an 11-year, single-institution experience comparing VATS versus an open approach in 107 consecutive pneumonectomies. Among patients chosen for VATS pneumonectomy, 16% were converted to open. Patients with later-stage disease made up a large proportion of the study; the final pathology was stage III or stage IV for 27% of all patients who underwent VATS and 38% of all open pneumonectomies. The authors recognize that there was likely selection bias, because the study was not randomized and surgeons would be more prone to offer VATS to patients who had earlier-stage, less-invasive tumors. In the open operations, patients received an R1, not R0, resection 23% of the time, compared with only 10% of the time in the VATS group, which suggests that patients who had more difficult resections, closer margins, and more invasive disease were offered open thoracotomies. The 30-day mortality rate was 7.5% for VATS and was 5.0% for open, but this difference was not statistically significant. Locoregional recurrence rates were 10% for both groups of patients, and recurrence at any site was 30% in the VATS group and 38% in the open group without any statistically significant differences. Patients with clinical stages III and IV disease who underwent pneumonectomy did not have different overall survival rates; the median survival was 60 months in patients who underwent VATS versus 41 months in those who underwent VATS but converted to open and 13 months in patients in the open group. There were also no differences in overall survival based on pathologic stages III and IV disease. Rates of median survival were 18 months in the VATS group, 41 months in the VATS-converted-to-open group, and 7 months in the open group. The longer survival times in patients whose were chosen to undergo VATS and then were converted to an open operation reveal the inherent selection bias in the study, because both groups ultimately had an open thoracotomy.[24] However, it appears that, in a select group of patients with later-stage III and IV disease, complication rates and long-term survival outcomes after VATS pneumonectomy were not inferior to those of open pneumonectomy.

At our institution, we favor an open thoracotomy for patients with stage IIIA lung cancer, because these patients with stage III disease have had previous chemotherapy and radiation. We believe that, in these patients, an open approach ensures a complete lymph node dissection and optimizes the opportunity for definite local control. Without a randomized, controlled trial, it is difficult to make unbiased outcome comparisons between VATS and open resections. However, it appears that, in experienced hands, long-term survival outcomes for carefully selected patients are no worse with VATS resection than for patients who undergo an open approach.

MOLECULAR PROFILING IN LATE-STAGE DISEASE

An interesting new area of research in the management of stage IIIA NSCLC is the molecular profiling of tumors to further stratify patients by risk. Most of the current literature surrounding genetic profiling in lung cancer has focused on predicting recurrence in early-stage disease, but similar assays may have prognostic value in later lung cancer stages as well. Molecular assays of biopsy specimens could be used preoperatively to help guide patient selection for surgery

FIGURE 1. Molecular Profiling Predicts Survival in Stage III Lung Cancer
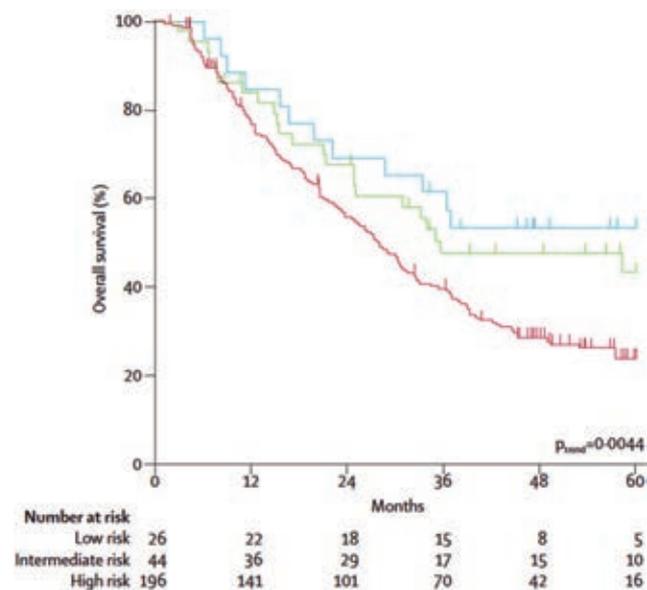
Analysis of nonsquamous stage III NSCLC tumors with a molecular assay divides patients into low, intermediate, and high risk groups on the basis of the genetic profiles of the tumors. Risk stratification by the molecular assay successfully predicts survival, with significant differences in 5-year overall survival rates (p = 0.0044). Prognostic assays such as this one may help guide future management of stage III NSCLC, but current data are limited and further investigation in this area is needed.[25]

and tumor biopsies, with high-risk profiles suggestive of ominous genetics, and imminent systemic disease could predict shorter survival times or the high likelihood for recurrence after surgery, which therefore would allow physicians to make more informed decisions about surgical candidacy.

A 14-gene expression assay was developed at our institution to stratify the mortality risk in nonsquamous NSCLC tumor specimens. This molecular assay has been internationally validated in more than 2,000 patients to predict disease recurrence and has repeatedly outperformed conventional staging criteria and high-risk NCCN clinicopathologic features.[25-28] Among a validation cohort from the China Clinical Trials Consortium that included 266 patients with stage IIIA disease who underwent an attempt at surgical resection, Kratz et al[25] demonstrated that there were significant differences in survival based on a tumor's genetic profile. Of these 266 patients, molecular profiling determined that 73% had high-risk tumors, 17% had intermediate-risk tumors, and 10% had low-risk tumors. The 5-year overall survival outcomes were significantly different between these groups, with only a 25% 5-year survival rate in high-risk patients compared with approximately a 50% 5-year survival rate in the low- and intermediate-risk groups (p = 0.0044; Fig. 1). The genetic profile of a tumor provides additional prognostic information to predict which patients within the same clinicopathologic stage are at higher risk of disease recurrence.[25]

Other studies have examined the use of markers from surgical pathology specimens to predict treatment response in later-stage disease. Shen et al[29] examined microRNA expression profiles in stages IIB and IIIA, fully resected, *EGFR*-mutant NSCLC and found that certain mRNA expression levels were predictive of disease recurrence, survival, and response to gefitinib.[29]

This is an emerging area of research, and much more work is still needed. However, preliminary studies are interesting and suggest that there is important prognostic information to be gained from genetic profiling of late-stage tumors. This information can predict recurrence or overall survival times within patients who have stage IIIA disease and also could be used to make more informed adjuvant treatment decisions. On preoperative biopsy specimens, patients with stage IIIA disease and favorable tumor genetics may be more likely to have limited local disease and, therefore, would benefit the most from local control with a surgical resection. Specific molecular assays might be developed to predict which tumors are most likely to be downstaged by induction therapy or to predict the response to certain chemotherapy or radiation regimens. As tumor mutation analysis and personalized medicine become the standard of care, patients with NSCLC will expect a more detailed tumor assessment, an individualized treatment plan, and an enhanced survival risk stratification.

CONCLUSION

Stage IIIA NSCLC includes a heterogeneous group of patients and an overall grim prognosis. Management of this stage involves separating patients who have curable local disease from those who essentially have early systemic disease. In appropriate surgical candidates, a complete a surgical resection provides optimal local control and has real survival benefits beyond chemotherapy and radiation alone. Surgical resections likely improve survival by removing the resilient and treatment-resistant cancer stem cell populations. Cancer stem cells make up a small percentage of all tumor cells and are unique in that they posses the qualities of self-renewal and pluripotency, a high proliferative capacity, and the ability to resist chemotherapy and radiation.[30] Tumor recurrence after dramatic responses to chemotherapy and radiation has been attributed to the lingering presence of isolated stem cells, which have the ability to repopulate an entire tumor after surviving treatment.[31] Eradication of this critical cell population is best achieved by removing any residual, microscopic tumor foci via a surgical resection after induction therapy.

The real future in managing stage IIIA disease lies in the development of better systemic therapies to successfully downstage tumors before obtaining definitive local control with a surgical resection. In addition, there is a need for improved prognostic molecular testing in later-stage tumors to help predict which patients will respond to induction therapy and to provide improved survival risk stratification after surgery. As these new technologies are developed, a multidisciplinary thoracic oncology team remains critical to make individualized treatment recommendations that optimize long-term survival.

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Relationships are considered self-held and compensated unless otherwise noted. Relationships marked "L" indicate leadership positions. Relationships marked "I" are those held by an immediate family member; those marked "B" are held by the author and an immediate family member. Institutional relationships are marked "Inst." Relationships marked "U" are uncompensated.

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Current Standards and Clinical Trials in Systemic Therapy for Stage III Lung Cancer: What Is New?

Nasser Hanna, MD

OVERVIEW

Patients with stage III non–small cell lung cancer (NSCLC) comprise a heterogeneous group, some of whom have curable disease. Although surgery plays a role for some patients, the majority of fit patients will be treated with chemotherapy and radiation alone. The optimal therapy for all patients remains undefined, but certain principles of care are widely accepted. Specifically, concurrent chemoradiation is the standard of care for patients who are able to tolerate such therapy, namely those with a good performance status, minimal or no weight loss, and adequate end-organ function, including pulmonary reserve. The most commonly used chemotherapy regimens given in combination with radiation therapy are cisplatin/etoposide or carboplatin/paclitaxel. Studies incorporating newer agents have not improved outcomes when compared to these older regimens. The merits of chemotherapy administered beyond the conclusion of radiation therapy continue to be debated, but thus far randomized phase III trials have not provided supporting evidence for this strategy. Incorporating antiangiogenics with chemoradiation has proven to be ineffective in some cases and unsafe in others. Studies with targeted agents in unselected patient populations with stage III disease have also been disappointing. Despite these recent setbacks, however, there remains a sound rationale for incorporating molecularly targeted agents into chemoradiation regimens in select patient groups or consolidating chemoradiation with immunotherapy. Studies that incorporate drugs targeting *EGFR, ALK, RAS*, programmed cell death 1 (PD-1), and programmed death ligand 1 (PD-L1) into the management of patients with stage III NSCLC will be reviewed.

Some patients with stage III NSCLC have curable disease, although the majority will die within 3 years. This variability in outcome is a result of the heterogeneity of clinical presentations, fitness of patients, and the biology of disease. Poor prognostic variables for toxicity and/or outcomes include decreased performance status, the presence of significant weight loss, N3 disease, increased number of lymph node stations involved, and the volume of lung that will receive at least 20 Gy (V_{20}) of radiation.[1-3] Challenges in treating this patient population include advanced age (median age older than 70) and the presence of multiple comorbidities which are related to chronic tobacco exposure, including compromised cardiopulmonary function. Therapeutic decisions in the advanced-stage setting are driven by tumor histology and the presence or absence of key genetic alterations. However, the integration of this knowledge into the treatment of patients with stage III disease has lagged behind.

ADVANCES IN THE TREATMENT OF PATIENTS WITH STAGE III NSCLC

Despite these obstacles, advances have been realized over the last 30 years in the treatment of patients with stage III NSCLC (Table 1).[4] For a subset of patients, surgery remains an inte-

gral part of therapy.[2,5] For the majority, radiation therapy is the backbone of treatment. Beginning in the 1980s, the integration of chemotherapy with radiation therapy prolonged survival and increased the cure rate compared with radiation therapy alone.[6,7] In the 1990s and early 2000s, the concurrent use of chemotherapy with radiation therapy proved modestly more effective than the sequential use of these modalities.[4] In addition, the routine use of PET imaging within the last 2 decades has aided in staging and radiation planning.

For fit patients with stage III unresectable or inoperable NSCLC who have adequate end-organ function including pulmonary reserve, an absence of other substantial comorbidities or weight loss, and a V_{20} less than 35%, concurrent chemoradiation is a standard of care.[4,8,9] However, the optimal choice of chemotherapy agents and the number of cycles to be given remains unsettled. Platinum-containing regimens are standard. Two cycles of cisplatin/vinblastine followed by radiation therapy proved to be superior to radiation therapy alone.[7] Subsequent studies have tested a platinum (P) agent with etoposide (E), mitomycin (M) plus vindesine (V), vinorelbine, irinotecan, paclitaxel, docetaxel, or pemetrexed.[8-13] Few trials have compared these regimens head-to-head and those that have report small therapeutic differences. The West Japan Thoracic Oncology Group (WJTOG) reported no substantial differ-

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TABLE 1. Key Historic Clinical Trials in Unresectable or Inoperable Stage III NSCLC

Group	Design	Comment
CALGB[7]	Chemotherapy→ XRT versus XRT	Established the role of sequential chemotherapy followed by radiation in stage III disease
WJLCG[9]	Concurrent ChemoXRT versus Sequential ChemoXRT	Demonstrated concurrent chemoradiation may be superior to sequential therapy
RTOG[8]	Concurrent ChemoXRT versus Sequential ChemoXRT	Confirmed the superiority of concurrent chemoradiation over sequential therapy
CALGB[16]	Chemotherapy → ChemoXRT versus ChemoXRT	Induction therapy prior to concurrent chemoradiation does not prolong survival compared to concurrent chemoradiation alone
HOG/USO[17]	ChemoXRT versus ChemoXRT → Chemo	Consolidation docetaxel does not improve survival compared to concurrent chemoradiation alone
South Korea[13]	ChemoXRT versus ChemoXRT → Chemo	Consolidation therapy utilizing cisplatin and docetaxel does not improve survival when added to weekly platinum/taxane/XRT
SWOG[21]	ChemoXRT → Chemo versus ChemoXRT → Chemo → Gefitinib	The addition of gefitinib as consolidation in an unselected patient population is potentially harmful
RTOG[12]	ChemoXRT versus ChemoXRT + Cetuximab	The addition of cetuximab to concurrent chemoradiation does not improve survival compared with concurrent chemoradiation alone

Abbreviations: NSCLC, non-small cell lung cancer; CALGB, Cancer and Leukemia Group B; XRT, external beam radiation therapy; WJLCG, West Japan Lung Cancer Group; Chemo, chemotherapy; RTOG, Radiation Therapy Oncology Group; HOG, Hoosier Oncology Group; USO, US Oncology; SWOG, Southwest Oncology Group.

ences in overall survival when comparing third-generation chemotherapy with second-generation chemotherapy.[10] A randomized study of radiation therapy combined with MVP, carboplatin/irinotecan, or carboplatin/paclitaxel reported comparable survival, but higher toxicity with MVP. A second study from Japan compared radiation combined with MVP or cisplatin/docetaxel.[14] Two-year survival rates favored cisplatin/docetaxel (p = 0.059), although grade 3 or 4 esophagitis were also higher in the docetaxel arm. A phase III trial investigating cisplatin/pemetrexed and radiation therapy followed by consolidation pemetrexed compared to PE with concurrent radiation followed by consolidation chemotherapy has been completed (NCT00686959). Although efficacy endpoints have not been reported, toxicity profiles differed modestly.[15] The most commonly used regimens in the United States are PE or carboplatin plus paclitaxel. A retrospective analysis within the Veterans Health Administration data of 1,842 patients treated with either regimen suggested comparable survival outcomes, although PE was associated with increased toxicities.[16] However, to date, a prospectively conducted randomized phase III trial comparing these two regimens has not been reported.

THE ROLE OF INDUCTION OR CONSOLIDATION CHEMOTHERAPY FOLLOWING CHEMORADIATION

The initial gains in survival with the addition of chemotherapy to radiation were appreciated in phase III studies utilizing only two cycles of chemotherapy.[7] This stands in contrast to the use of three cycles of chemotherapy given in the neoadjuvant setting, four cycles in the adjuvant setting, and four to six cycles of combination therapy followed by maintenance therapy in the metastatic setting. Therefore, additional attempts to improve outcomes have focused on delivering additional chemotherapy before (induction) concurrent chemoradiation or following (consolidation) concurrent chemoradiation. Each of these strategies has been extensively studied in phase II and III studies. Unfortunately, neither approach has clearly demonstrated improved survival times compared to concurrent chemoradiation alone. For example, a phase III study from the Cancer and Leukemia Group B randomly assigned patients to receive concurrent weekly carboplatin plus paclitaxel and radiation or the same therapy preceded by two cycles of full-dose carboplatin and paclitaxel.[17] No difference in overall survival was reported. Investigators from the Hoosier Oncology Group and US Oncology evaluated the role of consolidation docetaxel.[18] In this phase III study patients were treated with concurrent PE and 59.4 Gy of radiation and then randomly assigned (if their disease had not progressed) to receive docetaxel for three cycles or observation alone. No survival difference was seen, but patients receiving docetaxel had higher rates of pneumonitis and febrile neutropenia. More recently, Huber et al treated patients with concurrent cisplatin plus oral vinorelbine and radiation and then randomly assigned them to either consolidation cisplatin plus vinorelbine or best supportive care.[19] Progression-free and overall survival times were almost identical.

KEY POINTS

- Stage III non–small cell lung cancer comprises a heterogeneous group of patients.
- Concurrent chemoradiation is the standard of care for most fit patients with stage III disease.
- The optimal chemotherapy agents and duration of therapy remain undefined.
- Early results incorporating targeted agents or antiangiogenics have proven ineffective or, in some cases, unsafe.
- Newer strategies with molecularly targeted agents, including inhibitors of *EGFR*, *ALK*, *RAS*, and PD-1, are under investigation.

At the 2014 ASCO Annual Meeting, Park et al reported the results from their phase III trial testing consolidation therapy utilizing a platinum agent and a taxane.[13] All patients initially received weekly cisplatin and docetaxel with concurrent radiation followed by consolidation cisplatin and docetaxel versus observation alone. Although no survival difference was reported, patients receiving consolidation therapy experienced substantially more toxicity. A similar study design evaluating the role of consolidation carboplatin plus paclitaxel (versus observation) following weekly carboplatin and paclitaxel given concurrently with radiation has not been conducted. A pooled analysis of the literature which included 41 phase II or III studies indicated no improvement in survival (hazard ratio [HR] 0.94 for median survival time; p = 0.4) with any consolidation strategy, including using the same drugs in consolidation as were given with concurrent radiation, switching chemotherapy agents, or incorporating novel or molecularly targeted agents.[20]

Regardless of the drugs used, doses of radiation, or duration of chemotherapy, it appears we have reached a plateau in survival with current strategies in stage III NSCLC. Although the median survival time has improved in contemporary studies, the 3-year survival rates (a surrogate for long-term survival or even cure) are only 15% to 25%. Improvements in median survival may be attributed to better patient selection, stage migration, improved radiation techniques and supportive care, and greater experience by clinicians in treating this population of patients with concurrent chemoradiation.[21]

INITIAL ATTEMPTS AT INCORPORATING NOVEL AGENTS INTO CHEMORADIATION REGIMENS

Initial attempts to incorporate molecularly targeted therapies into chemoradiation have been disappointing thus far. A phase III study from the Southwest Oncology Group treated patients (irrespective of EGFR status) with PE plus radiation followed by consolidation docetaxel. Patients without progressive disease were randomly assigned to receive further therapy with gefitinib or placebo.[22] Overall survival favored placebo. More recently, a study led by the Radiation Therapy Oncology Group randomly assigned patients with stage III NSCLC to receive chemoradiation (60 Gy vs. 74 Gy; MST 28.7 vs. 20.3 months, HR 1.38, p = 0.004). with or without cetuximab. Survival times favored 60 Gy, and the addition of cetuximab provided no additional benefit.[12] Furthermore, attempts at incorporating antiangiogenic agents have proven to be ineffective or unsafe.[23-26]

NEWER STRATEGIES INCORPORATING MOLECULARLY TARGETED AGENTS INTO STAGE III NSCLC

Despite these early failures incorporating molecularly targeted agents into chemoradiation regimens, the scientific rationale to do so remains sound (Table 2). The initial trials evaluating EGFR targeting agents did not require patient se-

TABLE 2. Key Ongoing or Planned Clinical Trials in the United States in Unresectable or Inoperable Stage III NSCLC

Study Design	Schema	NCT Registry Number
Randomized phase II	Arm 1: Erlotinib→ ChemoXRT	01822496
	Arm 2: ChemoXRT (EGFR mut cohort)	
	Arm 3: Crizotinib→ ChemoXRT	
	Arm 4: ChemoXRT (ALK+ cohort)	
Randomized phase II	Following definitive treatment, consolidation with:	01909752
	Arm 1: Dribbles vaccine and HPV vaccine	
	Arm 2: Dribbles vaccine and HPV vaccine and imiquimod	
	Arm 3: Dribbles vaccine and HPV vaccine and GM-CSF	
Single-arm phase II	Following definitive ChemoXRT, consolidation with: tecemotide and bevacizumab	00828009
Randomized phase II	Arm 1: ChemoXRT followed by consolidation chemo	02186847
	Arm 2: Metformin X 14 d followed by ChemoXRT with metformin followed by consolidation with chemotherapy and metformin	
Phase I	ChemoXRT with trametinib followed by consolidation chemotherapy	01912625
Single-arm phase II	ChemoXRT followed by pembrolizumab	02343952
Randomized phase III	Following definitive ChemoXRT, consolidation with:	02125461
	Arm 1: MED14736	
	Arm 2: Placebo	

Abbreviations: NSCLC, non-small cell lung cancer; NCT, National Clinical Trial; Chemo, chemotherapy; XRT, external beam radiation therapy; mut, mutated; GM-CSF, granulocyte macrophage colony-stimulating factor; d, days.

lection based on the tumor molecular profile. Continued efforts to target the EGFR in stage III disease are underway. Radiation is known to increase the expression of EGFR, resulting in radiation resistance.[27] Proposed mechanisms for this include EGFR interaction with DNA repair enzymes; EGFR activation of PI3K/AKT signaling which suppresses DNA damage-induced apoptosis; and activation of downstream signaling through the RAS and STAT pathways to promote cancer cell repopulation. Furthermore, tumors with activating EGFR mutations appear to be more sensitive to radiation than their EGFR wild-type counterparts.[27,28] This may be because mutated EGFR fails to bind to a key enzyme in DNA repair. Similarly, in vitro studies suggest that cell lines that harbor ALK fusion proteins may be more sensitive to ALK inhibition combined with radiation.[29] In one experiment, the combination of crizotinib with radiation resulted in greater tumor growth inhibition than either treatment alone in a cell line with an ALK fusion protein. Similar effects were not seen in a cell line without the ALK fusion protein.

Based on this preclinical data, a study of erlotinib or crizotinib as induction therapy in patients with stage III NSCLC is ongoing (NCT 01822496). Approximately 234 patients with nonsquamous NSCLC will be stratified based on *EGFR* mutation and *ALK* gene-rearrangement status and randomly assigned to one of four arms. Patients on arm 1 and 3 receive erlotinib or crizotinib, respectively, as induction therapy for up to 12 weeks. Those who have no disease response after 6 weeks will undergo immediate chemoradiation. After 2 weeks of completion of induction therapy, patients receive concurrent chemoradiation with cisplatin and etoposide or carboplatin and paclitaxel. Patients on arm 2 (*EGFR* mutation cohort) or arm 4 (*ALK* gene-rearranged cohort) receive concurrent chemoradiation beginning on day 1. The primary objective is to assess whether patients treated with targeted agents based on molecular characteristics have a longer progression-free survival than those treated with chemoradiation alone.

The *RAS* oncogene has also been proposed to play a role in radiation resistance.[30] Although targeting *RAS* activation directly has yielded disappointing results, downstream targets of *RAS*, including *MEK*, may be feasible. In vitro studies demonstrate an increased radiosensitization when such downstream pathways are inhibited. It has also been proposed that PI3K is a mediator of *RAS*-induced radiation resistance. Efforts are underway within the National Cancer Institute to incorporate trametinib (NCT 01912625), a *MEK* inhibitor, into chemoradiation in patients with *KRAS* mutations. Approximately 30 patients with any histology NSCLC with a *KRAS* mutation in exons G12, G13, or Q61 will receive daily oral trametinib with concurrent carboplatin, paclitaxel, and radiation for 6 weeks followed by two cycles of consolidation carboplatin and paclitaxel alone. The primary objective is to determine the maximum tolerated dose of trametinib when combined with chemoradiation. Future efforts with PI3K inhibitors may also be worth testing.

IMMUNOTHERAPY IN STAGE III NSCLC

Targeting immune regulatory pathways has proven to be a successful strategy in NSCLC. A phase III study comparing nivolumab with docetaxel in patients with NSCLC was recently closed based on the recommendations of a Data and Safety Monitoring Board citing evidence of superior overall survival favoring nivolumab (CheckMate-017 trial, Bristol Myers Squibb press release January 11, 2015). Consolidating chemoradiation with an immunotherapy has been studied in stage III NSCLC. Tecemotide (L-bLP25), a MUC1-antigen–specific cancer immunotherapy, was evaluated as consolidation therapy after chemoradiation in a phase III randomized trial.[31] In this trial, patients were allowed to receive either concurrent or sequential chemoradiation. Although overall survival did not statistically differ between the two groups (HR 0.88, 0.75–1.03; p = 0.123), a subset analysis of 829 patients treated with concurrent chemoradiation favored the tecemotide arm (median survival, 30.8 vs. 20.6 months, HR 0.78; p = 0.016). Another trial

from the Eastern Cooperative Oncology Group, combining tecemotide with bevacizumab after chemoradiation, has recently completed accrual (NCT 00828009). Patients with stage III nonsquamous NSCLC received concurrent chemoradiation using weekly carboplatin and paclitaxel for 6.5 weeks. Patients with nonprogression receive two additional cycles of consolidation chemotherapy. On completion of consolidation chemotherapy, patients receive a single dose of cyclophosphamide 3 days before the first tecemotide and bevacizumab treatment. Patients then receive bevacizumab on day 1 and tecemotide subcutaneously on days 1, 8, and 15 for cycles 1 and 2 then every other cycle beginning in course 4. Treatment continues every 21 days for up to 34 cycles. The primary endpoint is to determine the safety of bevacizumab plus tecemotide as maintenance therapy in this setting.

Evidence indicates radiation therapy induces tumor antigen release from the dying tumor cells that can be recognized by the immune system.[32,33] Therefore, radiation is an immune stimulator that enhances T-cell activation and infiltration. Furthermore, radiation has been shown to increase the expression of PD-L1, an immune checkpoint. Combining radiation with checkpoint inhibitors, such as PD-1 or PD-L1 inhibitors, including MED14736, pembrolizumab, and nivolumab, are being investigated. MED14736, an antibody to PD-L1, will be tested in a phase III industry-sponsored trial (PACIFIC) involving 702 patients across 100 sites around the globe (NCT 02125461). Patients with unresectable stage III NSCLC will be treated with concurrent chemoradiation utilizing at least two cycles of platinum-based chemotherapy. If no evidence of progression is seen, patients will then be treated with MED14736 or placebo (2:1 randomization) for up to 1 year. The primary endpoint is overall survival. A phase II single-arm study evaluating pembrolizumab as consolidation therapy after concurrent chemoradiotherapy will be conducted by the Hoosier Cancer Research Network (NCT 02343952). In this trial, approximately 83 patients will receive either weekly carboplatin/paclitaxel or cisplatin/etoposide with 59.4 to 66 Gy radiation. Patients with nonprogressive disease will then receive pembrolizumab every 3 weeks for up to 1 year. A safety analysis will take place after the initial 10 patients have been treated and received at least three cycles of pembrolizumab. Given the possibility of pneumonitis after chemoradiation and the expected activation of T cells with pembrolizumab, the incidence of delayed or severe pneumonitis and/or recurrent esophagitis in the radiated field will be of special importance. The primary endpoint is to assess the time to distant relapse. Secondary analyses will evaluate the effect of PDL-1 status on outcomes. In addition, a randomized trial with nivolumab after chemoradiation is under development (personal communication, Jeffrey Bradley, February 2015).

CONCLUSION

Therapeutic advances in the treatment of stage III NSCLC are difficult to achieve. Many factors contribute to the diffi-

culty of this task. Valuable lessons have been learned from research over the last 3 decades. Namely, further manipulations of existing chemotherapy drugs are unlikely to provide substantial survival gains. The path forward will follow new science and new drugs. The recent success with targeted agents and immunotherapy in the metastatic setting provides encouragement that similar success is possible in the stage III setting, where cures are still possible.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked "L" indicate leadership positions. Relationships marked "I" are those held by an immediate family member; those marked "B" are held by the author and an immediate family member. Institutional relationships are marked "Inst." Relationships marked "U" are uncompensated.

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LYMPHOMA AND PLASMA CELL DISORDERS

Diffuse Large B-Cell Lymphoma: Are We Ready for Molecular Subtype-Specific Therapy?

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ABC, GCB, and Double-Hit Diffuse Large B-Cell Lymphoma: Does Subtype Make a Difference in Therapy Selection?

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OVERVIEW

Personalized therapy for the treatment of patients with cancer is rapidly approaching and is an achievable goal in the near future. A substantial number of novel targets have been developed into therapeutic agents. There is a substantial variability to antitumor activity by novel therapeutics because of the unique heterogeneity and biology that exists both between and within lymphoma subtypes. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL). Approximately 40% of patients have refractory disease or disease that will relapse after an initial response, and the majority of patients with relapsed DLBCL will succumb to the disease. There are two major biologically distinct molecular subtypes of DLBCL: germinal center B-cell (GCB) and activated B-cell (ABC). ABC DLBCL is associated with substantially worse outcomes when treated with standard chemoimmunotherapy. In addition to GCB and ABC subtypes, double-hit lymphomas (approximately 5% to 10% of patients) and double-expressor lymphomas, which overexpress *MYC* and BCL2 protein, are aggressive DLBCLs and are also associated with a poor prognosis. Double-hit lymphomas have concurrent chromosomal rearrangements of *MYC* plus *BCL2* (or less likely, *BCL6*). Advances in molecular characterization techniques and the development of novel agents targeting specific subtypes of DLBCL have provided a foundation for personalized therapy of DLBCL based on molecular subtype. A number of early clinical trials evaluating combinations of novel targeted agents with standard chemotherapy (R-CHOP) have been completed and have demonstrated the feasibility of this approach with encouraging efficacy. As such, molecular classification of DLBCL is not only important for prognostication, but moves to center stage for personalization of therapy for DLBCL.

The addition of the anti-CD20 monoclonal antibody rituximab (R) to the standard CHOP regimen consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) was a major breakthrough in the front-line treatment for patients with DLBCL, resulting in dramatic improvements in progression-free survival (PFS) and overall survival (OS).[1-3] However, despite these improvements approximately 40% of patients with DLBCL who are treated with R-CHOP or R-CHOP–like chemotherapy will relapse or develop refractory disease,[4,5] and the majority of patients with relapsed or refractory DLBCL will succumb to the disease.[1-3] Various strategies have been implemented to improve the outcome of DLBCL, including intensification of chemotherapy and use of maintenance therapy. Regardless of molecular subtype, standard front-line treatment for DLBCL is a combination of R-CHOP or CHOP-like chemotherapy.

Additional regimens and immunochemotherapy combinations are under investigation as alternatives to front-line R-CHOP, including dose-dense R-CHOP14, dose-adjusted R-EPOCH (rituximab plus etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin), and R-CEOP90 (rituximab, cyclophosphamide, etoposide, vincristine, prednisone).[6-8] In a

phase III trial including 1,080 patients with previously untreated DLBCL, no additional clinical benefit was observed in patients treated with R-CHOP every 14 days (R-CHOP14) versus every 21 days (R-CHOP21).[6] Although evaluation of some of these intensification strategies is still ongoing, recent insight into the biology of DLBCL allowed the development of strategies based on the addition of novel agents (X) to R-CHOP in so-called XR-CHOP combinations[9] that target specific oncogenic pathways (Fig. 1). In the development of these strategies, molecular characterization of DLBCL and the development of biomarkers is a critical step to identify patients who might benefit from the addition of novel agent(s). Indeed, because of the molecular heterogeneity of DLBCL, addition of a novel agent may benefit only a subgroup of patients with DLBCL. In this regard, preclinical and clinical studies of novel agents as monotherapies in relapsed and refractory DLBCL often provide important initial indications regarding the subtype of DLBCL that might benefit from specific targeted therapy.

Gene expression profiling (GEP) of DLBCL resulted in the identification of two major and clinically distinct subtypes that are classified based on cell of origin (COO) and are as-

sociated with differences in clinical outcome: GCB and non-GCB, which is further comprised of ABC and primary mediastinal B-cell types.[10,11] DLBCL subtypes have striking differences in clinical outcome, with the ABC DLBCL subtype being associated with poor outcome. Until recently, COO classification of DLBCL had little influence on clinical practice. However, COO classifications have become more clinically relevant as a result of two major factors: (1) the development of new real-time COO assessment methods, including immunohistochemistry (IHC) and Nanostrings technology and (2) the identification of novel agents with activity in a specific DLBCL subtype (particularly ABC DLBCL).

CLASSES OF AGENTS WITH MOLECULAR SUBTYPE-SPECIFIC ACTIVITY CURRENTLY IN DEVELOPMENT FOR THE TREATMENT OF DLBCL
Agents Predominantly Active in Non-GCB (ABC) DLBCL

The majority of novel agents in development as front-line treatment for DLBCL appear to specifically target the ABC subtype of DLBCL, through either the B-cell receptor (BCR) pathway or pathway(s) downstream of the BCR pathway. This review will include only agents that are already in advanced clinical trials.

Proteasome inhibitors. Proteasome inhibitors play a key role in suppression of the transcription factor nuclear factor kappa B (NFκB), a critical pathway downstream of the BCR

pathway that is constitutively activated in ABC DLBCL.[12] Use of the first-generation proteasome inhibitor bortezomib as monotherapy generated no responses in patients with relapsed/refractory DLBCL despite good preclinical evidence of possible activity. Bortezomib combined with DA-EPOCH (dose-adjusted etoposide, vincristine, doxorubicin, with cyclophosphamide and prednisone) chemotherapy yielded a complete response (CR) of 18% and a partial response (PR) of 16%,[13] and demonstrated a significantly higher response (83% vs. 13%; p < 0.001) and median OS (10.8 vs. 3.4 months; p = 0.003) in ABC DLBCL compared to GCB DLBCL, respectively.

Immunomodulatory agents. Immunomodulatory drugs (IMiDs) are structural and functional analogs of thalidomide that have immunomodulatory, antiangiogenic, and antitumor functions.[14] Preclinical studies show that IMiDs modulate antibody synthesis; regulate the production of certain subsets of T cells (T-helper cells); inhibit the production of cytokines, including tumor necrosis factor alpha (TNFα); induce G_0/G_1 cell cycle arrest; and decrease angiogenesis through the suppression of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF).[15] In vivo and in vitro experiments have shown that the IMiD lenalidomide functions in DLBCL through multiple mechanisms, for example by enhancing antibody-dependent cell-mediated cytotoxicity (ADCC), inhibiting the production of proinflammatory cytokines such as TNFα, decreasing NFκB activity, and arresting DNA synthesis.[16-18] The effect of single-agent lenalidomide was investigated in 217 patients with aggressive relapsed/refractory NHL as part of an international phase II study. Median PFS and response duration in the DLBCL subpopulation were 2.7 months and 4.6 months, respectively.[19] In a retrospective analysis of two phase II trials (NHL-002 and NHL-003), patients with aggressive relapsed/refractory NHL who received single-agent lenalidomide and prior autologous stem cell transplantation (ASCT) were compared with those who did not receive ASCT. Thirty-four patients (39%) with relapsed or refractory NHL and prior ASCT therapy responded to lenalidomide (objective response rate [ORR] 39%), including patients with DLBCL (ORR 29%).[20] In an ongoing, randomized, phase II/III clinical trial, the safety and efficacy of lenalidomide in relapsed/refractory DLBCL is being compared to the Investigator's choice (gemcitabine, oxaliplatin, rituximab, or etoposide) (NCT01197560).[21]

B-cell receptor signaling pathway inhibitors. The BCR complex and associated protein tyrosine kinases are important for normal B-cell function and antibody production. Constitutively activated BCR signaling is linked to the initiation and maintenance of B-cell malignancies, including involvement in the pathogenesis of the ABC subtype of DLBCL.[22] The BTK inhibitor ibrutinib was investigated in 70 patients with relapsed/refractory DLBCL as part of a multicenter, open-label, phase II trial. Among 60 patients who were evaluable for response, the ORR was 22% (5% CR) and PFS was 1.6 months.[23] In a phase II study, 23 patients treated with the

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KEY POINTS

- The activated B-cell (ABC) subset of diffuse large B-cell lymphoma (DLBCL) is biologically distinct, characterized by clonic B-cell receptor signaling, and associated with poor outcomes when treated with a standard therapy. Activation of the clonic B-cell receptor pathway allows for therapeutic targeting.
- Targeted agents in relapsed DLBCL can be combined with R-CHOP in front-line therapy of DLBCL. Since most of these agents are active in ABC DLBCL, many ongoing studies select patients who have this subset.
- The germinal center B-cell (GCB) subset of DLBCL is associated with better outcomes and may require different therapeutic approaches.
- Double-hit lymphoma (DHL) is responsible for a substantial number of relapses in GCB DLBCL (DHL is usually a GCB phenotype). All newly diagnosed DLBCL biopsy samples should be tested for DHL by fluorescent in situ hybridization and by immunohistochemistry for double-expressor DLBCL and, whenever possible, patients should be referred to participation in clinical trials.
- Off-study treatment of DHL should be dose-intense whenever feasible, with current data supporting the use of dose-adjusted R-EPOCH plus central nervous system prophylaxis until more effective novel targeted agents for this lymphoma subtype are developed.

FIGURE 1. Pathways Targeted By Treatments Currently in Development for Patients with DLBCL
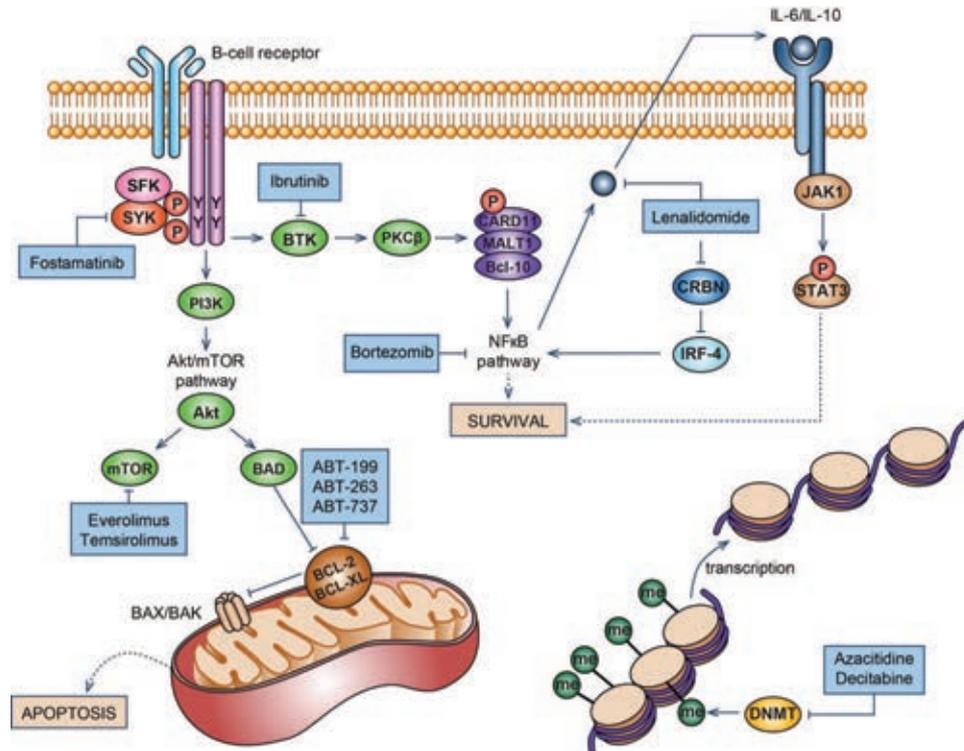
Abbreviations: AKT, protein kinase B; BAD, BCL2-associated death promoter; BAK, BCL2 antagonist killer; BAX, BCL2-associated X protein; BCL, B-cell lymphoma; BTK, Bruton's tyrosine kinase; CARD11, caspase recruitment domain family, member 11; CRBN, cereblon; DLBCL, diffuse large B-cell lymphoma; Me, methylation; DNMT, DNA methyltransferase; JAK1, Janus kinase 1; IL, interleukin; IRF-4, interferon regulatory factor 4; MALT1, mucosa-associated lymphoid tissue lymphoma translocation protein 1; MTOR, mammalian target of rapamycin; P, phosphorylation; NFκB, nuclear factor kappa B; PI3K, phosphoinositide 3-kinase; PKC-beta, protein kinase C beta; SFK, Src family kinase; STAT3, signal transducer and activator of transcription 3; SYK, spleen tyrosine kinase.

spleen tyrosine kinase (SYK) inhibitor fostamatinib demonstrated a median PFS of 2.7 months and achieved an ORR of 22%.[24]

AGENTS WITH POTENTIAL ACTIVITY IN GCB DLBCL

Although patients with GCB DLBCL have better outcomes than patients with the ABC subtype, approximately 20% of patients with the GCB subtype of DLBCL relapse following R-CHOP or R-CHOP—like chemotherapy and DLBCL relapse is associated with poor outcomes regardless of molecular subtype. Several agents show potential activity in the GCB subtype of DLBCL, among which BCL2 inhibitors are the best studied to date. Importantly, DLBCL with concurrent *MYC* and *BCL2* or *BCL6* translocation, known as double-hit DLBCL,[25] is associated with very poor outcomes and is usually the GCB subtype by molecular profiling. Double-hit DLBCL represents approximately 5% of de novo cases of DLBCL, and is responsible for approximately a quarter of all relapses in GCB DLBCL. Treatment of this particularly high-risk lymphoma is discussed later.

BCL2 inhibitors. Prevention of apoptosis is one mechanism through which cancer cells continue to survive. Unlike most oncogenes that promote proliferation, members of the antiapoptotic B-cell lymphoma-2 (BCL-2) family of proteins (BCL-2, BCL-XL, BCL-w, MCL-1, BFL1/A-1, and BCL-B)

suppress apoptosis through interaction with, and inactivation of, proapoptotic proteins such as BH3.[26] In contrast to most agents active in ABC DLBCL, which appear to have low activity in the GCB subtype, BCL2 inhibitors might be active in both ABC and GCB DLBCL. Whereas in the GCB subtype BCL2 is often overexpressed as a result of translocation, some patients with the ABC subtype appear to overexpress BCL2 at the protein level.[27] ABT-737 and its oral equivalent ABT-263 target multiple antiapoptotic members of the BCL-2 family, including BCL-2, BCL-XL, and BCL-w, whereas ABT-199 potently and selectively inhibits BCL-2, thereby sequestering the proapoptotic proteins and facilitating death of malignant cells.[26,28,29]

FRONT-LINE TREATMENT: XR-CHOP
Bor-RCHOP

A combination of the proteasome inhibitor bortezomib and R-CHOP (VR-CHOP or Bor-RCHOP) was evaluated in patients with previously untreated DLBCL or mantle cell lymphoma. The evaluable ORR was 100%; 86% of patients exhibited CR or CR unconfirmed (CRu). In the intent-to-treat (ITT) population of 40 patients, ORR was 88%, and 75% had CR/CRu. The 2-year PFS was 64% and 2-year OS was 70%.[30] A current randomized phase II trial is designed to compare the effect of VR-CHOP versus R-CHOP on PFS (NCT00931918),[31] and an ongoing randomized phase III

trial is investigating the efficacy of CHOP versus RV-CHOP in patients with DLBCL (REMoDL-B; NCT01324596).[32]

R2-CHOP

Patients treated with the immunomodulatory agent lenalidomide (R) in combination with R-CHOP (R2-CHOP) achieved ORRs and CRs of 90% to 100% and 77% to 86%, respectively, in phase I and phase II trials.[33-36] In one phase II trial, the most frequent grade 3/4 hematologic adverse events (AEs) included neutropenia (31%), leukocytopenia (28%), and thrombocytopenia (13%); no grade 4 nonhematologic AEs were reported.[36] Response to R2-CHOP in patients with GCB versus non-GCB DLBCL was similar in a phase II trial (32 tissue samples available), and the 2-year PFS was 71% and 81%, respectively.[36] Interestingly, in a separate phase II trial involving patients with newly diagnosed DLBCL who were treated with R2-CHOP, the 2-year OS was 75% for patients with GCB DLBCL compared with 83% for non-GCB subtypes. In patients treated with R-CHOP alone, a 2-year OS of 78% and 46% was achieved in GCB and non-GCB subgroups, respectively, suggesting that the addition of lenalidomide can improve the poor prognosis usually reported in the non-GCB population in response to standard R-CHOP therapy (Fig. 2).[37]

A randomized phase II trial designed to evaluate the effect of R-CHOP versus R2-CHOP in patients with newly diagnosed DLBCL (NCT01856192) is ongoing.[38] A separate phase III study (ROBUST) evaluating R2-CHOP versus R-CHOP in patients with ABC DLBCL as defined by GEP is currently open. Real-time GEP with a turnaround time of 5 business days or less is used to assess patient eligibility for this trial.

IR-CHOP

The Bruton's tyrosine kinase (BTK) inhibitor ibrutinib has been investigated in combination with R-CHOP (IR-CHOP) in a phase Ib, nonrandomized, open-label trial in 33 patients with newly diagnosed DLBCL, mantle cell lymphoma, or follicular lymphoma. At the interim evaluation, the ORR was 100% (CR 64% and PR 36%) in 22 patients with DLBCL. The most common all-grade AEs reported in all patients were neutropenia (67%), nausea (67%), thrombocytopenia (61%), vomiting (48%), and anemia (36%).[39] Additionally, a randomized, double-blind, phase III study is currently comparing event-free survival in patients treated with IR-CHOP versus R-CHOP (NCT01855750).[34]

TREATMENT FOR RELAPSED/REFRACTORY DLBCL

In the Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study, 396 patients with relapsed/refractory CD20+ DLBCL were randomly selected to receive either rituximab, ifosfamide, etoposide, and carboplatin (R-ICE),

FIGURE 2. Outcomes of Patients Treated with R-CHOP or R2-CHOP according to GCB versus Non-GCB DLBCL Subtype
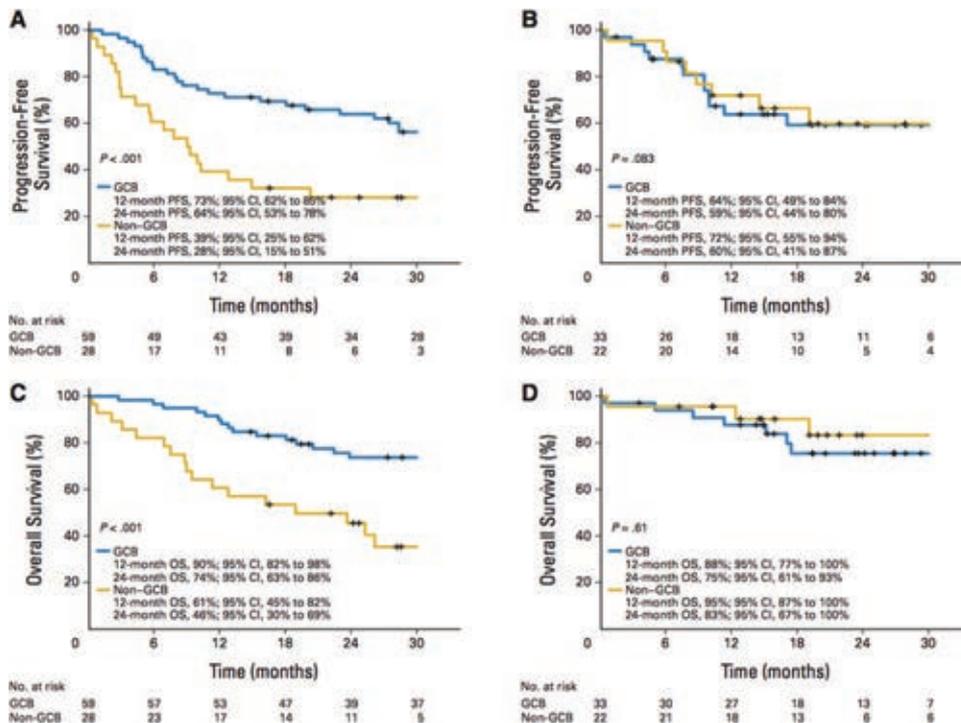
Outcomes are shown for historic control patients treated with R-CHOP and study patients treated with R2CHOP based on germinal center B-cell (GCB) versus non-GCB diffuse large B-cell lymphoma (DLBCL) subtype. (A) Progression-free survival in patients treated with R-CHOP for non-GCB versus GCB DLBCL. (B) Progression-free survival in patients treated with R2CHOP for non-GCB versus GCB DLBCL. (C) Overall survival in patients treated with R2CHOP for non-GCB versus GCB DLBCL. (D) Overall survival in patients treated with R2CHOP for non-GCB versus GCB DLBCL.

TABLE 1. Agents with Differential Single Agent and in Combination of XR-CHOP Activity in DLBCL Subtypes

Agent	Combination	No. of Patients	Phase	ORR (%)		CR (%)		PFS (%)		OS (%)	
				GCB	ABC/NGCB	GCB	ABC/NGCB	GCB	ABC/NGCB	GCB	ABC/NGCB
Front-Line											
Lenalidomide [36]	R-CHOP	32	II	88	88	81	88	71	81	88	94
Lenalidomide [37]	R-CHOP	64	II	–	–	–	–	59	60	75	83
	R-CHOP*			–	–	–	–	64	28	78	46
Relapse/Refractory											
Bortezomib [13]	DA-EPOCH	44		13	83	6	42	3.4	10.8	9.5	5.8
Lenalidomide [42]	–	40	II	9	53	4	24	1.7	6.2	13.5	14
Ibrutinib [23]	–	70	II	5	40	0	8	1.3	2.5	–	–

Abbreviations: ABC, activated B-cell typeCR, complete response; DA-EPOCH, dose-adjusted etoposide, vincristine, doxorubicin, with cyclophosphamide and prednisone; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell type; NGCB, non-GCB type; mo, month; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, prednisone; XR, addition of novel agents to R-CHOP.
*R-CHOP without lenalidomide.

or rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP). Patients whose disease relapsed early (< 1 year) following front-line rituximab chemotherapy had a very poor prognosis, with a 3-year PFS of 20% compared with 45% for patients whose disesase relapsed after 1 year.[40]

MYC-POSITIVE AND DOUBLE-HIT DLBCL

MYC is a transcription factor associated with a number of cellular functions (e.g., cell growth and proliferation, angiogenesis, protein synthesis, metabolism, and DNA replication) with a strong oncogeneic potential.[42] In human B-cell neoplasms, *MYC* rearrangements involving the t(8;14) is a hallmark in Burkitt lymphoma and present in the majority of cases. Typically, it is a primary genetic event and presents as a simple karyotype and the sole chromosomal abnormality in this aggressive subtype of B-cell lymphoma. *MYC* gene rearrangements have also been identified in other lymphoid neoplasms, including: DLBCL (7% to 14%), unclassifiable B-cell lymphoma (35%), plasmablastic lymphoma (50%), plasma cell myeloma (15% to 50%), and mantle cell lymphoma (26 patients). Of interest, in non-Burkitt lymphoma histologies, *MYC* rearrangements are found as part of a complex karyotype and typically represent secondary genetic events.[42-43] *MYC* gene activation in DLBCL can occur via translocation (5% to 14%), copy gain (19% to 38%), amplication (2%), or mutation (32%).[44-47] In general, *MYC* rearrangement predicts an inferior outcome in DLBCL, but it is not clear whether it is because of *MYC* rearrangement itself or because 58% to 83% of MYC-translocated DLBCL also have concurrent dual or triple translocation with *BCL2* and/or *BCL6* (less likely) identified as double-hit or triple-hit DLBCL.[42,48-49] These patients often have 12 months or less OS when treated with R-CHOP.[50]

Of note, high MYC-protein expression (28% to 41%) of DLBCL without *MYC* gene abnormalities has been identified (suggesting alternate mechanisms of MYC induction). Patients with DLBCL with a high percentage of both MYC and BCL2 protein (20% to 44%) expression by IHC staining carry a poor prognosis; treatment with standard R-CHOP or CHOP-like immunochemotherapy results in inferior PFS and OS on retrospective

analyses.[51-54] Many studies have defined these patients as having double-expressor DLBCL, and most studies require that tumor cells express at least 40% MYC and at least 50% to 70% BCL2 positivity. Although patients with double-expressor DLBCL (DEL) have a worse prognosis than those without double expression of MYC plus BCL2, it should be noted that different studies utilize variable cutoff points to define positivity. Unlike the reproducibility of the fluorescent in situ hybridization (FISH) technique, the IHC technique is less robust and has more variability associated with it. Interestingly, the majority of double-hit DLBCL (DHL) (defined here as having *MYC* + *BCL2* rearrangements) is primarily GCB-like, whereas DEL is primarily ABC-like. This unique observation leads us to question whether a successful therapeutic approach in DHL will be equally successful in DEL based on differences inherent within the COO and likely differences in cellular/molecular pathways, genetics, and variable-resistance pathways. Only large prospective clinical trials utilizing central path review of FISH, as well has IHC, and well-defined inclusion definitions of positivity will be able to answer this question.

CURRENT TREATMENT APPROACH: OVERVIEW

As mentioned previously, R-CHOP is an inadequate induction therapy for DHL (i.e., most patients die within 2 years of diagnosis). The malignant DHL neoplastic cell attains an amazing survival advantage. Concurrent *MYC* + *BCL2* translocations confer increased cell growth, cell cycle transit, and metabolism and/angiogenesis via MYC, but at the same time increased antiapoptosis (i.e., drug resistance) via BCL2. In general, DHL patients often present with several poor prognostic characteristics: median age in the seventh decade (many unable to tolerate dose-intensive therapeutic approaches); stage III/IV disease; high-intermediate/high (HI/H) IPI; elevated LDH; high frequency of extranodal sites (including the central nervous system).[55-56] Various multidrug therapy regimens with or without rituximab have been utilized to treat DHL, including dose-intensive therapies that have curative potential in BL, although published data from retrospective reviews do not indicate any single optimal induction therapy approach (Table 2). Patients achieving a

TABLE 2. DHL Induction Therapy and Outcome

Reference	No. of Patients	Treatment	Outcome (Median)	Comments
Petrich et al[50]	311	R-CHOP (32%)	PFS: 10.9; OS: 21.9 mo	Median follow-up: 23 mo
		R-Hyper CVAD/MA (21%)	PFS (R-CHOP): 7.8 mo versus 26.6 mo (for any "intensive" regimen; p = 0.001)	No difference between intensive regimens
		R-EPOCH (21%)		Consolidative SCT: no improvement in OS in CR patients (p = 0.14)
		R-CoDox-M/IVAC (14%)		
Oki et al[60]	129 (93 with both MYC and BCL2 translocation)	R-CHOP	2-yr EFS	Increased OS with R-EPOCH c/w R-CHOP (p = 0.057)*
		R-Hyper CVAD/MA	Overall: 33% (overall)	
		R-EPOCH	R-CHOP: 25%	
			R-Hyper CVAD/MA: 32%	CNS involvement: 13% at 3 yrs
			R-EPOCH: 67%	
			CR	
			R-CHOP: 20%	
			R-EPOCH: 68%	
			R-Hyper CVAD/MA: 70%	
Johnson et al[61]	54	CHOP-like (43%)	OS	BCL2 protein–negative cases (more favorable)
	BCL-U (36 patients)	R-CHOP (20%)	R-CHOP: 1.4 yr	
	DLBCL (17 patients)	HDT (11%)	CHOP: 5 mo	
		Palliative (26%)		
Li et al[62]	BCL-U (33 patients)	R-CHOP (39%)	OS: 18.6 mo	Median age: 55
	DLBCL (23 patients)	R-Hyper CVAD/MA (57%)		Aggressive chemotherapy nor SCT associated with increased PFS/OS

Abbreviations: BCL-U, B-cell lymphoma, unclassifiable with features intermediate between DLBCL and BL; R, rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; Hyper CVAD/MA, hyper-fractionated cyclophosphamide, doxorubicin, vincristine, dexamethasone/methotrexate, cytarabine; EPOCH, etoposide, prednisone, doxorubicin, cyclophosphamide, doxorubicin; CoDox-M/IVAC, cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, cytarabine; PFS, progression-free survival; OS, overall survival; SCT, stem cell transplant.
*Consolidative SCT in 50% R-EPOCH versus 4% R-CHOP group.

complete remission with regimens more intensive than R-CHOP had better PFS, but consolidative SCT did not seem to improve OS in these patients. Of the regimens utilized, R-EPOCH: (1) has curative potential in BL, (2) is better tolerated than more dose-intensive (DI) regimens, and (3) appears to have at least similar efficacy compared to DI therapies. In addition to the data from Oki et al (Table 2), a meta-analysis of 401 DHL patients by Howlett et al[57] presented at the 2014 American Society of Hematology (ASH) Annual Meeting demonstrated R-EPOCH (and more DI regimens) were associated with improvement in PFS (but not OS) compared to R-CHOP. Another presentation at ASH 2014 by Dunleavy et al[58] utilizing R-EPOCH in a multicenter phase II study, which included DHL, demonstrated a promising early PFS (87% at 14 months).

Currently consolidative autologous SCT in chemotherapy-sensitive patients (especially CRs) does not appear to signifi-

TABLE 3. Novel Future Therapeutic Considerations

Agent	Comment	Reference
ABT-199	Platelet-sparing BCL2 inhibitor (BH$_3$-mimetic)	28, 63
BET bromodomain inhibitors (JQ1, I-BET 151, OTX015)	Down-regulation of MYC-associated transcription: Decreased cell proliferation and inhibition of MYC-driven neoplasms	64–66
CAR-T cells	Autologous T-cell-mediated killing of CD19-positive lymphoid neoplasms	67, 68
Aurora kinase inhibitors (alisertib)	Aurora kinase function is required for tumor maintenance of MYC-driven lymphoma	69, 70
mTor inhibition	mTOR may plan an important role in tumor maintenance by MYC in B lymphocytes	71, 72
MLN9708/Ixazomib (second generation proteasome inhibitor)	Preclinical model: Degraded MYC and can induce lymphoma cell death at nanomolar concentrations	73
PI3K inhibition	High percent GCB-DLBCL cases: loss of PTEN → activation of PI3K/AKT pathway → MYC upregulation	74
Inhibition of human mitochondrial peptide deformylase	Causes apoptosis in MYC-overexpressing hematopoietic neoplasms	75
SIRT4 protein	Suppresses tumor formation in MYC-induced B-cell lymphoma models	76

Abbreviations: mTOR, mammalian target of rapamycin; GCB, germinal B cell; DLBCL, diffuse large B-cell lymphoma.

cantly change clinical outcomes. This may likely be a result of the inherent rapid tumor cell growth and inherent drug-resistant DHL cells that remain after induction therapy (i.e., minimal residual disease) that would likely not be cured with a high-dose, chemotherapy-based conditioning regimen typically utilized during autologous stem cell transplantation. Of interest, review of the literature identified two abstracts, which included a total of approximately 50 patients, that concluded that patients with DHL who undergo allogeneic SCT following dose-intensive induction therapy have prolonged OS.[57,59] Unfortunately, several reasons make it unlikely that allogeneic SCT will make a major effect in the future treatment of a significant percentage of DHL patients: (1) limited data from a small number of selected patients, (2) the risk of relapsed disease while awaiting graft-versus-lymphoma to occur, (3) the need for a suitable HLA-compatible donor, and (4) the risk of chronic graft-versus-host disease.

The future holds promise that novel targeted agents, which either directly or indirectly inhibit MYC and BCL2, will lead to improved overall survival in patients with DHL (Table 3). Many agents have demonstrated in vitro and in vivo animal antitumor activity, and a limited number are in early human clinical trials. It is quite likely that DHL will require a rational combination of MYC/BCL2 inhibitors in combination with effective chemotherapeutic agents (e.g., BH_3-mimetics will resensitize cells to drug toxicity, etc.) to optimize the killing of these highly resistant lymphoma cells and change DHL from one of the worst subtypes of DLBCL into a therapeutically responsive subtype (with a significant improvement in clinical outcomes). Based on the information provided above, all newly diagnosed DLBCL tumor biopsies should undergo FISH and IHC evaluation to identify DHL and DEL, respectively. These patients, whenever possible, should be referred to participation on clinical trials. Off study, the use of R-EPOCH induction (including central nervous system prophylaxis) is a reasonable approach while we await further testing and validation of effective novel targeted agents to be added to our current therapeutic armamentarium against DHL.

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Cell-of-Origin in Diffuse Large B-Cell Lymphoma: Are the Assays Ready for the Clinic?

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OVERVIEW

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma worldwide and consists of a heterogeneous group of cancers classified together on the basis of shared morphology, immunophenotype, and aggressive clinical behavior. It is now recognized that this malignancy comprises at least two distinct molecular subtypes identified by gene expression profiling: the activated B-cell-like (ABC) and the germinal center B-cell-like (GCB) groups—the cell-of-origin (COO) classification. These two groups have different genetic mutation landscapes, pathobiology, and outcomes following treatment. Evidence is accumulating that novel agents have selective activity in one or the other COO group, making COO a predictive biomarker. Thus, there is now a pressing need for accurate and robust methods to assign COO, to support clinical trials, and ultimately guide treatment decisions for patients. The "gold standard" methods for COO are based on gene expression profiling (GEP) of RNA from fresh frozen tissue using microarray technology, which is an impractical solution when formalin-fixed paraffin-embedded tissue (FFPET) biopsies are the standard diagnostic material. This review outlines the history of the COO classification before examining the practical implementation of COO assays applicable to FFPET biopsies. The immunohistochemistry (IHC)-based algorithms and gene expression–based assays suitable for the highly degraded RNA from FFPET are discussed. Finally, the technical and practical challenges that still need to be addressed are outlined before robust gene expression–based assays are used in the routine management of patients with DLBCL.

Diffuse large B-cell lymphoma is the most frequent non-Hodgkin lymphoma (NHL), making up about 30% to 40% of diagnoses of NHL worldwide.[1] It is increasingly recognized that DLBCL represents a heterogeneous group of malignancies that have previously been grouped together on the basis of a shared morphology, immunophenotype, and aggressive clinical behavior.[1] The standard of care for patients with DLBCL, established over a decade ago, is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) immunochemotherapy. This "one-size fits-all" approach results in cure for 50% to 60% of patients.[2,3] However, the outcomes for those that experience disease progression or relapse are poor, making identification of this clinical subgroup and improving their up-front treatment a major priority for the field.

A major step toward precision medicine in DLBCL was taken 15 years ago, when examination of the gene expression of DLBCL tumors revealed previously unrecognized molecular heterogeneity in this malignancy.[4] The resulting COO classification divided tumors into those with gene expression reminiscent of germinal center B cells (the GCB group) and those with gene expression similar to activated B cells (the ABC group). The division of DLBCL tumors into these two groups has provided a scaffold on which a substantial amount of

our current understanding of the DLBCL pathobiology is now organized. Additionally, DLBCL COO is a strong prognostic biomarker[4-6] identifying patient groups with substantially different outcomes following treatment. Finally, over the last decade, clinical observations and our evolving knowledge of the biology of the disease has led to the realization that the COO subtypes respond differentially to therapeutic agents.[7] Thus, COO is potentially a predictive biomarker that will soon be used to guide clinical management. This has cast the spotlight on our ability to accurately and reliably assign COO to patients' tumors. This review will focus on the assays that have been developed to determine COO, focusing on those applicable to routinely produced FFPET biopsies, addressing a central question: are these assays ready to guide clinical management?

FROM DEFINING DLBCL COO TO A PREDICTIVE BIOMARKER
Discovery of the Molecular Subtypes of DLBCL
In 2000, Alizadeh et al used gene expression profiling to explore the notion that unrecognized molecular heterogeneity in DLBCL underlies the heterogeneity in clinical behavior.[4] They used "Lymphochip" complementary DNA (cDNA) mi-

croarrays, covering a broad range of genes expressed by lymphoid cells and others suspected of being involved in cancer and immunology, to compare the gene expression profiles of lymphoid tumors against profiles from normal lymphoid cells.[4] Using hierarchical clustering (a method of grouping tumors together based on similarity of gene expression), it was shown that there were at least two distinct groups within DLBCL. The first group, which was designated as GCB, was characterized by high expression of genes expressed in normal B cells from the germinal center. The second group showed very low expression of these germinal center B cell genes, but high expression of genes normally expressed by activated B cells and was thus named ABC DLBCL. Importantly, these groupings explained some of the clinical heterogeneity in DLBCL, as patients with ABC DLBCL experienced substantially worse outcomes compared with patients with GCB DLBCL.

This work was expanded by the Leukemia Lymphoma Molecular Profiling Project (LLMPP), by applying the same microarray technology to a larger cohort of patients.[5] Hierarchical clustering, using the 100 genes that were most highly differentially expressed between GCB and ABC, identified three clusters within DLBCL: the aforementioned GCB and ABC, and a third group of cases that had gene expression that fell between these two groups, which they named "type 3." With cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) chemotherapy (the standard at that time), this group of patients had outcomes similar to those with ABC DLBCL. This type 3 nomenclature gave the impression that this was a biologically distinct third group of tumors. In hind-

sight, it is possible this group contained some cases that had low tumor content and some cases that were later identified as primary mediastinal B cell lymphoma.[8] What is clear is that when, in further studies, such cases were carefully removed, about 10% to 15% of DLBCL tumors remained that did not convincingly fall into either ABC or GCB categories––these cases are now labeled "unclassified."

The COO Algorithm

The LLMPP rapidly realized that in order for COO to be accurately assigned by other groups, there needed to be shift away from both the vagaries of hierarchical clustering and a microarray chip that was not commercially available. In 2003, Wright et al defined an algorithm that allowed classification of individual cases.[9] This algorithm was based on 27 genes on the Lymphochip microarray that were the most discriminatory between GCB and ABC, with these genes having both high fold-change differences between the two groups and also high variance in expression over the DLBCL population. These characteristics underlie the robustness of this algorithm even when other technology platforms are used to determine gene expression.

The algorithm produces a linear predictor score (LPS) using an equation that sums the gene expression of each gene multiplied by individual gene coefficients. Normal distributions of LPS scores were constructed for the ABC and GCB groups and then, for a given LPS score, a probability is assigned indicating whether that individual case is best allocated to the ABC or GCB group (Fig. 1). If the probability of the case being an ABC is over 90% it is designated ABC, and if the probability of being an ABC is less than 10% (i.e., greater than 90% chance of being a GCB) the case is called a GCB. This approach produces an "unclassified" group (roughly 10% to 15% of the tumors), in which the tumor cannot be assigned to either GCB or ABC with sufficient confidence. Although this would appear to be an undesirable feature of the algorithm, it has a distinct advantage when producing robust assays for COO. In a binary system, where there is no unclassified group, small shifts in the LPS, which could occur on retesting a tumor or testing it with a different technology, would lead to a shift from ABC to GCB, or vice versa. The unclassified group, by producing a buffer zone between ABC and GCB, minimizes the chances of a tumor being frankly misclassified (e.g., an ABC tumor labeled a GCB).

Fourteen of the initially selected 27 genes are present on commercially available Affymetrix microarray chips (Fig. 1) and an adjusted algorithm including just those 14 genes provides very similar results to the full algorithm.[9] The LLMPP have subsequently further refined the algorithm to include approximately 180 genes present on Affymetrix microarrays,[6] although the increase in accuracy over the 14-gene model is incrementally small. GEP on fresh frozen tissue with COO assignment using these algorithms is now widely considered to be the "gold standard" and, because of the robustness of the algorithm, is likely producing acceptable consistency of COO assignment across research groups. The caveat to this is that the accurate deployment of the

KEY POINTS

- Diffuse large B-cell lymphoma comprises at least two distinct molecular subtypes, defined by gene expression profiling, with different mutation landscapes, outcomes following treatment, and responses to novel targeted agents: the activated B-cell–like and germinal center B-cell–like cell-of-origin groups.
- Accurate and robust cell-of-origin assignment applicable to routinely produced formalin-fixed paraffin-embedded tissue biopsies is critically needed to support clinical trials and, ultimately, to guide disease management.
- The immunohistochemistry-based algorithms cannot currently be deployed with sufficient reproducibility or accuracy to support their use to guide clinical decision-making.
- A number of gene expression–based assays applicable to formalin-fixed paraffin-embedded tissue biopsies have been described with two of these assays now supporting patient selection in phase III randomized controlled trials of targeted agents.
- It is anticipated that a robust, accurate gene expression–based assay will be widely available by the time substantive evidence is produced that cell-of-origin should be used to guide initial treatment decisions in the clinic.

FIGURE 1. The Original Algorithm for Assigning COO
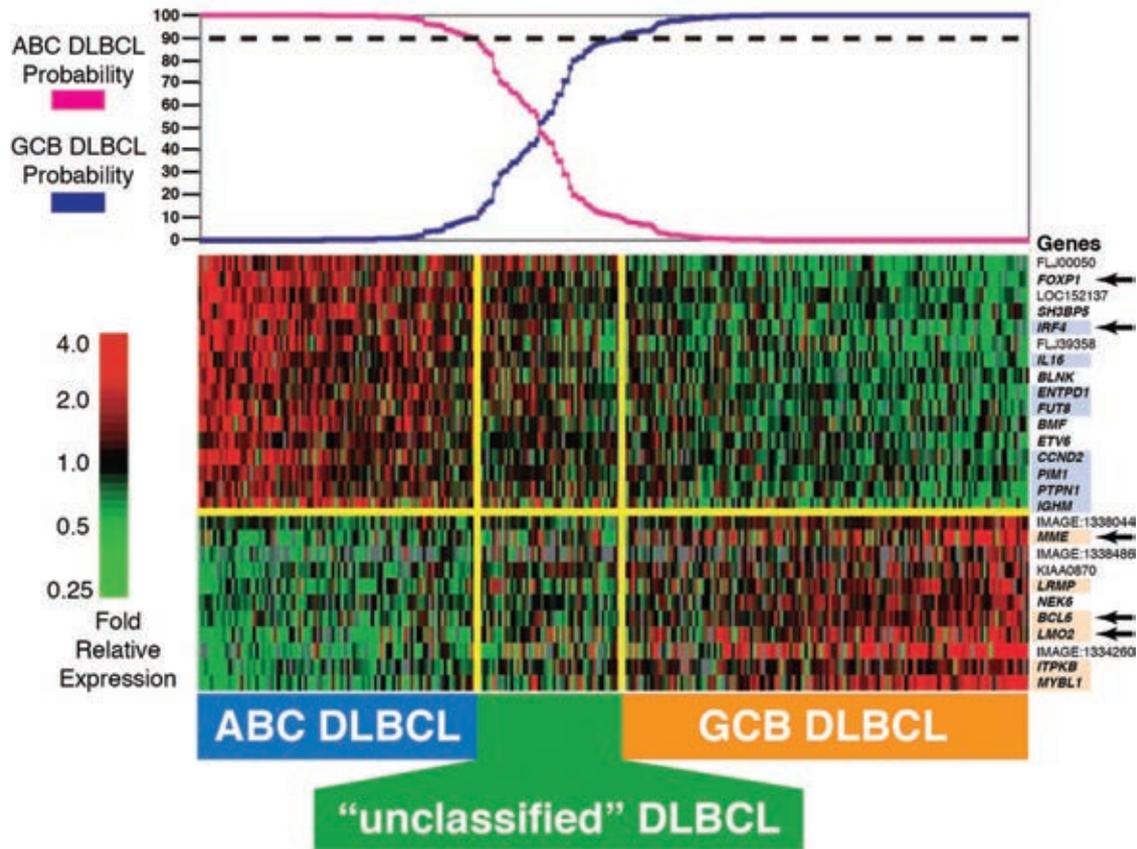
The model is shown in the form of a heatmap of gene expression data from 274 fresh frozen tissue biopsies using the Lymphochip microarray. Each column represents the relative gene expression of a tumor. The rows are the 27 genes that contribute to the model's linear predictor score (LPS). The 14 genes that were also present on the commercially available Affymetrix microarrays are highlighted in blue (overexpressed in ABC DLBCL) and orange (overexpressed in GCB DLBCL). Arrows designate genes, where antibodies against their corresponding protein have been used in immunohistochemistry-based COO assays. For an individual LPS score, a probability is determined as to whether the tumor is likely to be part of the ABC group or the GCB group (shown at top). Tumors with a probability of being ABC greater than 90% are considered ABC, whereas those with a probability of less than 10% are considered GCB.

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Wright algorithm requires that gene expression data are normalized back to that of the original cohort used to define the algorithm, which is a process that requires a large number of tumors that have a similar proportion of ABC and GCB as the original cohort. This error-prone process means that the position of the unclassified group is likely differently located across research groups, producing (subtly) different proportions of ABC, unclassified, and GCB DLBCL.

COO Defines Biologically Distinct Groups

Since the observation that gene expression could separate tumors into the two COO groups, ample evidence has emerged that these are, indeed, distinct biologic groups (recently reviewed by Shaffer et al[10]) classified together based on shared morphology. Targeted genetic examination[11-15] and subsequent genome-wide studies[16-20] have revealed an array of genetic aberrations that are heavily enriched, or exclusive to either ABC or GCB DLBCL. It has emerged that ABC DLBLC is characterized by constitutive activation of NF-κB, through chronic active B cell receptor signaling and/or aberrant Toll-

like receptor signaling, in concert with a differentiation block preventing maturation beyond the plasmablast stage. Although a straightforward schema is yet to emerge in GCB DLBCL, mechanisms providing a similar block to differentiation are present preventing maturation beyond the germinal center B cell.[21] The GCB and ABC gene expression signatures largely reflect the presence of these differentiation blocks, with the tumor cells continuing to express remnants of the gene expression program of normal germinal center B cells or plasmablasts, respectively.

The separation of DLBCL into ABC and GCB groups explains a substantial proportion of the heterogeneity seen in the genetic mutation landscape of DLBCL. However, it should be appreciated that there is still marked heterogeneity even when ABC and GCB are considered as separate diseases.[16-18] This is reflected when considering COO as a prognostic biomarker. As a group, patients with GCB DLBCL have superior outcomes following R-CHOP immunochemotherapy.[6] Hidden heterogeneity is implied by the observation that those patients known to have the poorest prognosis, being those with translocations involving *MYC* and *BCL2* (so-

called double-hit lymphoma) are almost exclusively GCB DLBCL. Correlation between genetic aberrations and outcomes after R-CHOP treatment within ABC and GCB groups is the subject of ongoing research.

COO as a Predictive Biomarker

From the clinical perspective, the observations and research linking COO with response to therapeutics are particularly exciting, holding the promise of improved patient outcomes. In some cases, this linkage is based on determining COO retrospectively in clinical trials searching for previously unsuspected differential efficacy across the COO groups,[22,23] in which the mechanism for these observations are yet to be explained. At the other end of the spectrum are therapeutic agents that are highly likely to only have efficacy in one or other of the COO groups based on their established mechanism of action.[7]

Accurate and reliable assays for COO are critically needed to allow patient selection for clinical trials of these agents, enriching for patients likely to truly benefit. Ultimately these assays will be needed to guide treatment decisions in the standard clinical management of patients with DLBCL. In order for an assay to be suitable for this task, it needs to be applicable to the FFPET biopsies routinely produced in the diagnostic process and have a rapid turnaround time.

TRANSLATION TO PRACTICAL TECHNOLOGY PLATFORMS

The gold standard methods originally described to assign COO rely on fresh frozen material and microarray technology. These methods are impractical for routine use in clinical trials, let alone standard clinical practice. Reflecting the importance of reliably assigning COO in the clinic, considerable efforts have been made to approximate the results of the gold standard method using practical technology platforms including IHC and methods for gene expression quantitation using RNA derived from FFPET.

IHC-Based Assays

The wide availability and familiarity of pathologists with IHC makes assays based on this technology highly desirable. In 2004, Hans et al developed an IHC-based algorithm applicable to FFPET biopsies that aimed to replicate the COO assignments made using GEP on fresh frozen tissue with the Lymphochip microarray.[5,24] A tissue microarray (TMA) was produced comprising FFPET from 152 de novo DLBCL tumor, with 142 of these having matching GEP results. IHC was performed with antibodies against CD10 (HUGO designation MME), BCL6, MUM1 (HUGO designation IRF4), CCND2, and FOXP1—five proteins that are highly differentially expressed between ABC and GCB (Fig. 1). No one single IHC stain was sufficient to accurately assign COO and a sequential algorithm was developed using CD10, BCL6, and MUM1 (Fig. 2) to separate GCB DLBCL from non-GCB DLBCL, with the latter group including both ABC DLBCL

and unclassified cases. Against the GEP gold standard, the Hans classifier correctly assigned 112 of the 142 tumors, a concordance of 79%. The authors emphasized that the groupings identified showed similar separation of outcomes after chemotherapy as the GEP-based groupings.

Since then, a number of other IHC-based algorithms have been described.[25-30] Choi et al[25] incorporated an additional newly developed antibody against GCET1 (HUGO designation SERPINA9), which is a protein highly expressed in germinal center B cells. They trained a sequential IHC algorithm (Fig. 2) using FFPET biopsies on TMAs against COO assignments that had been made on matching fresh frozen tissue using the Lymphochip microarray.[5] The assay was then validated using an independent group of 63 tumors that had matching GEP COO assignment with Affymetrix arrays. The reported concordance between the IHC-based assay and GEP in the validation cohort was 88%. Meyer et al[26] recognized that the sequential nature of these algorithms may be discarding important information that could be captured if the results of the stains were tallied up, thus producing the "Tally" algorithm (Fig. 2). A tie-breaker—if the scores supporting ABC were equal to those supporting GCB—was provided by staining for an antibody to LMO2, which is a protein that is highly expressed in germinal center B cells. Trained against COO assigned by GEP using Affymetrix microarrays on matched fresh frozen tissue, they reported a concordance of 93% in the training cohort. Finally, Visco et al[27] trained an IHC-based algorithm using 431 FFPET tumor biopsies on TMA using GEP on FFPET, rather than fresh frozen material, as the gold standard. They also reported a 93% concordance with COO by GEP and, similar to the Tally algorithm, this awaits confirmation in an independent validation cohort. A perceived weakness of these three studies is that they up-front excluded cases that were unclassified by GEP in both the training of the algorithms and calculations of performance. Three other studies have used antibodies that stain proteins that are differentially expressed between ABC and GCB DLBCL to produce assays that are prognostic in DLBCL.[28-30] It is important that these assays not be considered as COO assays as they were trained against outcome to treatment and not against a COO gold standard.

The described performance of these assays (Fig. 2) appeared very promising. However, a number of studies have highlighted issues regarding reproducibility and accuracy of IHC-based assays for COO. The Lunenburg Lymphoma Biomarker Consortium examined the reproducibility and reporting of a number of IHC stains, including for CD10, BCL6, and MUM1.[31] TMAs were distributed to eight laboratories for IHC staining and reporting. The level of agreement across the laboratories was poor, with agreement between laboratories for COO being 57% with a κ statistic (which corrects for agreement due to chance) of 0.36. Although CD10 staining and scoring was quite robust, there was poor agreement for both BCL6 and MUM1. The BCL6 stain appears to be very sensitive to different laboratory techniques, especially antibody detection. When a single laboratory performed the stains optimally, the pairwise agreement between reporting

FIGURE 2. Immunohistochemistry-Based Assays for COO Assignment
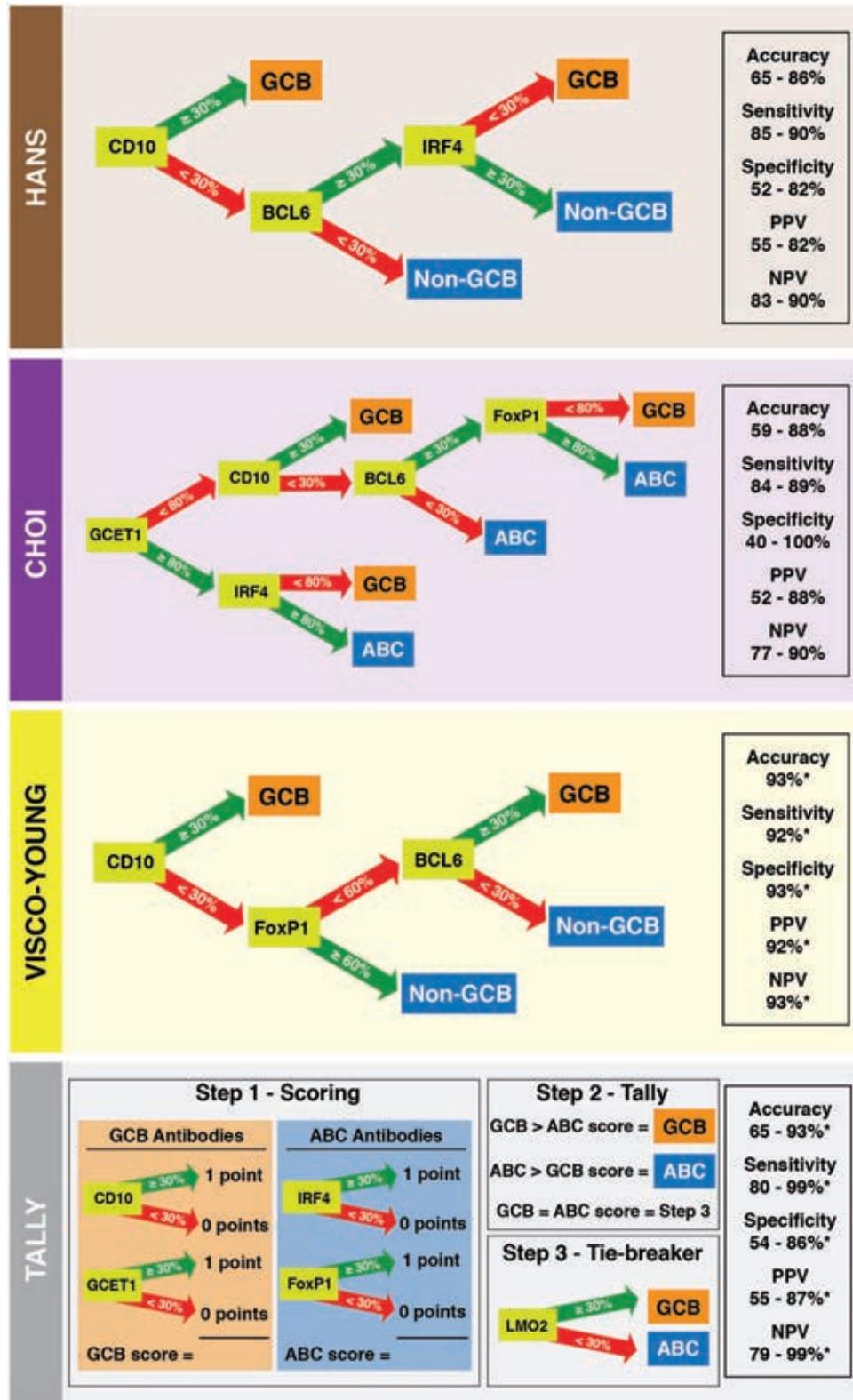
The four immunohistochemistry-based algorithms that were trained against gold standard gene expression profiling are shown. Accuracy is defined as the concordance with the gold standard. Sensitivity and specificity are shown for the ABC subtype—as they are binary assays, the specificity for ABC is the sensitivity for GCB, whereas the sensitivity for ABC is the specificity for GCB. The positive predictive value (PPV) and negative predictive value (NPV) are for the ABC subtype. The performance values are determined from independent validation cohorts, except where marked with an *, where they are from the training cohort and thus may overestimate the performance of the assay.

pathologist improved. However, the level of agreement with regards to COO was still suboptimal at 77% (κ statistic of 0.62). This level of agreement was improved if stains were excluded if no positive internal control was seen, but this resulted in a substantial rise in the failure rate of the assays. In response to the technical issues identified with BCL6, it has been suggested that the Hans and Choi classifiers be modified to exclude the BCL6 antibody.[26] More recently, Coutinho et al[32] examined the level of agreement across the IHC-based assays showing that the concordance between the assays was generally low. The study of Gutiérrez-Garcia et al directly addressed the accuracy of the IHC-based assays comparing the COO assignments by the Hans, Choi, and Tally algorithms with those from GEP on matched fresh frozen tissue using Affymetrix microarrays.[33] The results were disappointing, with concordance rates between 59% and 65% for the three IHC-based assays compared with the gold standard. The issues with reproducibility and the variable agreement with the gold standard COO likely play major roles in the observation that, although COO by GEP is prognostic in the R-CHOP era, the literature is highly discordant when COO is assigned by IHC-based assays. A meta-analysis of the IHC-based studies and the GEP-based studies has recently been published illustrating this point.[34]

In aggregate, despite the careful studies that defined the assays and the wide availability of IHC, the accumulated evidence indicates that IHC-based methods are not ready to guide clinical care at this time. If IHC-based assays are to be used to make management decisions, there will have to be a shift away from individual laboratory–developed tests and toward defined kits, where standardized antibodies, laboratory techniques, and agreement on scoring may improve reproducibility and accuracy, with reproducible observer scoring representing the most formidable obstacle to standardize. This approach is currently being used with the Hans algorithm providing the patient selection for a phase III, randomized, controlled trial assessing the efficacy of adding ibrutinib to R-CHOP in non-GCB DLBCL (ClinicalTrials.gov Identifier NCT01855750).

Gene Expression–Based Assays

Over the last decade, technologies have been developed that allow GEP employing the highly degraded RNA that is extracted from FFPET. Since 2010, a number of GEP-based assays have been described capitalizing on these advances. The generally high degree of accuracy of these assays is a testament to the very distinct gene expression patterns between ABC and GCB, and the robustness of the COO algorithm on which most of these assays are based.

The first demonstration of robust COO assignment using GEP on RNA from FFPET came from techniques that make this degraded RNA suitable for GEP using standard microarray technology. Williams et al compared the results of applying the Wright algorithm to GEP using RNA from FFPET compared with that of matched fresh frozen tissue.[35] When unclassifiable cases were excluded, there was one frank misclassification out of 44 cases, giving a concordance of 98%.

This approach has subsequently been used to assign COO in a large cohort of patients with de novo DLBCL treated with R-CHOP,[27] with the expected survival difference observed between the GCB and ABC groups.

A range of other technology platforms have subsequently been used as the basis of COO assays, including quantitative nuclease protection assay,[36] multiplex reverse transcription (RT)–polymerase chain reaction (PCR),[37-39] DASL,[40] and NanoString.[41-43] In studies in which the comparator was the gold standard of GEP in fresh frozen tissue, concordance was typically high at approximately 95%, when unclassified cases are removed.[36,37,41,43] Two studies will be discussed in more detail below as these assays are now supporting phase III randomized controlled trials.

Barrans et al have developed an assay for DLBCL COO based on the cDNA-mediated Annealing, Selection, extension, and Ligation (DASL) platform (Illumina, San Diego, CA), which provides genome-wide GEP in degraded RNA samples.[40] This technology, in combination with a new tool for COO assignment based on balanced voting between four machine-learning tools,[44] was used to assign COO in a population-based cohort of 172 patients with DLBCL.[40] The COO assignments in this population were 48% GCB, 31% ABC, and 21% type 3 (presumably equivalent to unclassified). Although there was no comparison with the gold standard COO assignment from fresh frozen material, the characteristics of the ABC and GCB groups were consistent with previous reports, with inferior outcomes following treatment in the ABC group. This assay is currently being used to stratify patients for a phase III, randomized, controlled trial assessing the efficacy of adding bortezomib to R-CHOP in patients with DLBCL (ClinicalTrials.gov Identifier NCT01324596). The randomization to the treatment arms, stratified by COO to ensure equal proportions of patients with ABC and GCB in each arm, occurs after one cycle of R-CHOP to allow patients to commence treatment in a timely fashion while awaiting the GEP results.

The LLMPP used the NanoString platform to develop a parsimonious gene expression–based COO assay for RNA from FFPET.[43] We took advantage of the ability of this platform to quantitate up to 800 RNA species in multiplex to build a model that most accurately replicated the larger GEP model described in Lenz et al.[6] In brief, 93 genes that were most differentially expressed between ABC and GCB on Affymetrix microarray data from fresh frozen tissue were quantified in RNA extracted from matched FFPET biopsies on the NanoString platform. Genes were then selected based on the degree of correlation of the expression between the two platforms (and across the sources of RNA). In total, 15 genes (Fig. 3A) were sufficient to accurately replicate the model from Lenz et al[6] with the addition of further genes resulting in negligible increase in assay accuracy. The low-density assay, comprising only these 15 genes and five house-keeping genes, was applied to samples that contributed to the training of the Lenz et al model, the final model was built and then "locked." This assay, named the Lymph2Cx, was then tested

FIGURE 3. The Lymph2Cx Assay: A Gene Expression-Based Assay for COO
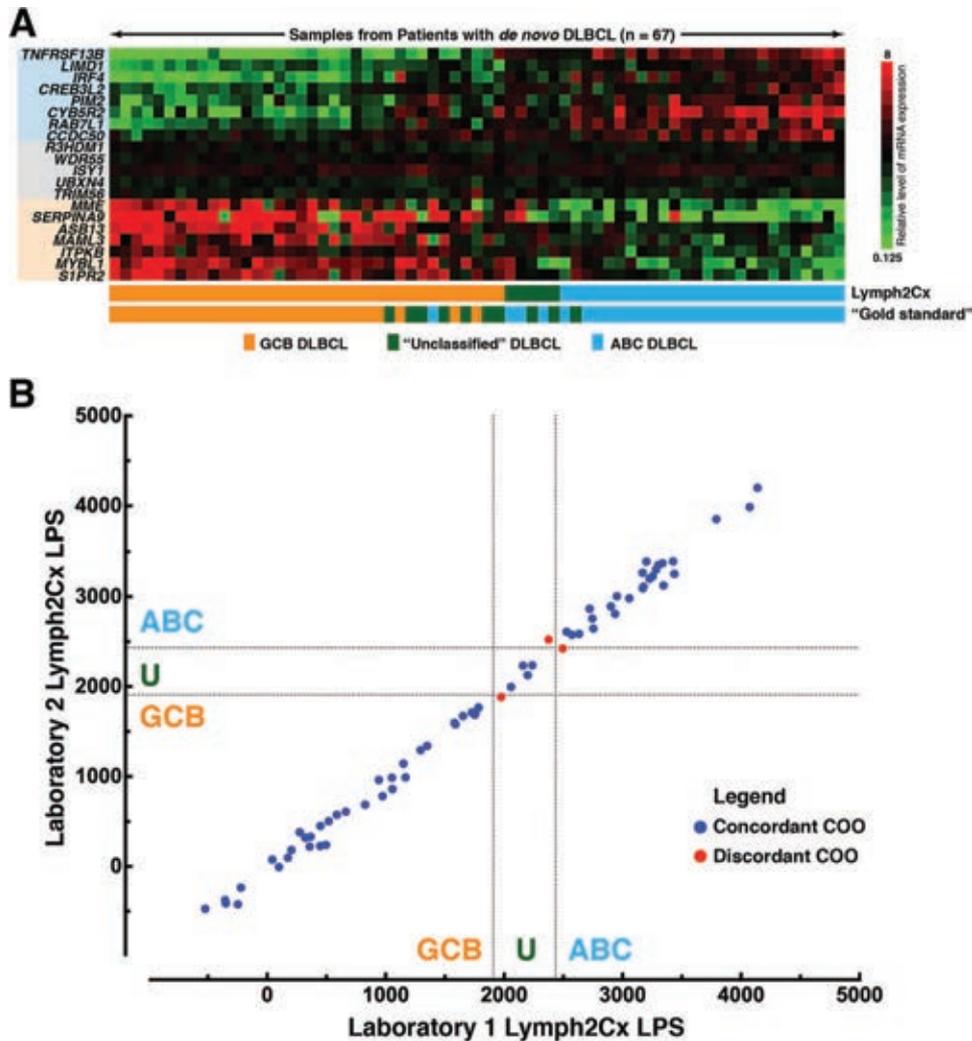
Panel A: The assay in the form of a heatmap from the independent validation cohort. The rows represent the 20 genes in the assay, with those highlighted in blue being overexpressed in the ABC group and those in orange being overexpressed in the GCB group. Genes in the middle are the house-keeping genes used to normalize for the number of quantifiable RNA species present. The columns are the relative gene expression of the 67 patients, arrayed from left to right based on ascending values of the assay's linear predictor score (LPS). Below the heatmap is the assignment according to the Lymph2Cx assay, with the gold standard assignments, from gene expression profiling from matched fresh frozen tissue using microarrays, at the bottom.

Panel B: Comparison of the LPSs from the Lymph2Cx assay between two independent laboratories. As indicated, lower LPS values indicates an assignment of GCB, whereas higher scores indicate an assignment of ABC. The concordance between the two sites was 95% (63 out of 66 cases) with no case being frankly misclassified (i.e., an ABC assigned GCB, or vice versa).

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in an independent cohort of 68 FFPET biopsies from the validation cohort of Lenz et al cases that have never contributed to COO model building. Compared with the gold standard, only one case was frankly misclassified (ABC to GCB) and the assay had a similar rate of unclassified cases to the gold standard. The Lymph2Cx was tested across two independent laboratories and showed 95% agreement of COO assignment, with discordant cases having shifted from a definitive assignment to unclassified, or vice versa (Fig. 3B). To the author's knowledge, this is the only published data addressing interlaboratory performance of the gene expression–based COO assays. The Lymph2Cx has subsequently been applied to FFPET biopsies from a population-based cohort of patients with de novo DLBCL, displaying a low failure rate of 1%, an unclassified rate of 11%, and substantial separation of

outcomes following R-CHOP between the ABC and GCB groups.[45] The assay has now been developed into a companion diagnostic by NanoString and is used to select patients for inclusion in a phase III, randomized, controlled trial assessing the efficacy of adding lenalidomide to R-CHOP in patients with ABC DLBCL (ClinicalTrials.gov Identifier NCT02285062). The rapid turnaround time of the assay is allowing randomization before starting treatment.

The unclassified category identifies tumors in which COO cannot be assigned with sufficient confidence. It is anticipated that clinical trials testing novel agents will be designed to include or exclude these patients by weighing the potential, albeit uncertain, benefits against the expected toxicities of the therapeutic. However, it is possible that patients with unclassified DLBCL will be left in a therapeutic wasteland,

where no agents have been specifically trialed in this group. This will particularly be an issue with assays that assign larger proportion of tumors in this category. It is hoped that the use of assays that provide more uniform and consistent COO assignment that we will be able to determine the genetic mutation landscape of unclassified cases and ascertain whether they represent a unique biologic group.

Ongoing Challenges for Gene Expression–Based Assays

In order for gene expression–based assays to be broadly and reliably deployed, a number of challenges need to be addressed. The first is the interlaboratory performance of the assays, which has only been demonstrated for the Lymph2Cx assay.[43] The second is the provision of adequate tissue for these assays. With the growing trend toward core needle biopsies for diagnosis of lymphoma, in many cases the biopsy material is exhausted in the routine diagnostic work-up. For these assays to be applicable to all patients, there will need to be a move back toward excisional biopsies and/or dedicated cores taken for molecular studies. Finally, most of these assays require the purchase and standardization of specialized equipment. It is anticipated that substantive evidence demonstrating the clinical and financial benefit of accurately determining DLBCL COO will be needed for the widespread adoption of these technologies.

ENVISAGING THE NEAR FUTURE

Although there is an expectation that eventually treatment of DLCBL will be guided by a comprehensive analysis of the genetic aberrations found in the tumor cells, the huge complexity that has been uncovered by genome-wide studies indicates that this will not be realized in the short-term or maybe even the medium-term. The first step toward precision medicine in DLBCL is the recognition that it comprises at least two distinct entities, as identified 15 years ago. The accurate and reliable ascertainment of COO in this disease will provide important enrichment for patients that will benefit from targeted therapeutics. It is anticipated that further genetic analyses will be performed on patients that do not respond to these agents to identify determinants of drug resistance.

At this point in time, there are no assays for COO assignment that can reliably inform treatment decisions outside of clinical trials. However, I firmly believe that by the time there is substantive evidence that new targeted agents improve patient outcomes, robust gene expression–based assays will be in place to identify the patients that will benefit.

ACKNOWLEDGMENT

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LYMPHOMA AND PLASMA CELL DISORDERS

Incorporating Novel Agents into Lymphoma Therapy: Value in Everyday Practice

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Novel Treatments for T-Cell Lymphoma

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OVERVIEW

T-cell lymphomas are a biologically and clinically diverse collection of diseases that collectively account for 10% to 15% of non-Hodgkin lymphomas. Unlike B-cell lymphomas, the response of T-cell lymphomas to standard anthracycline-containing chemotherapy regimens is suboptimal and the prognosis of patients is accordingly poor. To address these shortcomings, there has been a proliferation in biologic agents with novel mechanisms of action that target surface antigens, signaling pathways, or cellular processes. Given the large number of candidate molecules showing preclinical promise and the rarity of these diseases, drug development for peripheral T-cell lymphoma is challenging. We provide an overview of agents that have recently been approved for relapsed/refractory T-cell lymphoma and highlight efforts to introduce these agents into front-line treatment protocols in combination with chemotherapy. We discuss biologic doublets currently being evaluated as "chemotherapy-free" salvage regimens and highlight some of the most promising investigational agents in early clinical development.

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of diseases that account for 10 to 15% of non-Hodgkin lymphomas (NHLs) in most Western countries. Although the WHO 2008 classification system includes 22 distinct mature T-cell and natural killer (NK) cell neoplasms,[1] they can be functionally grouped according to typical presentation as nodal, extranodal, leukemic, and cutaneous (Fig. 1). Three entities account for approximately 60% of T-cell lymphomas: PTCL not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and systemic anaplastic large cell lymphoma (ALCL), which may be positive or negative for anaplastic lymphoma kinase (ALK).[2] For the purpose of this review, we will focus primarily on these most common subtypes.

CURRENT TREATMENT OUTCOMES

Unfortunately, the majority of patients with PTCL do not experience durable remissions following multiagent chemotherapy. The exception is patients with ALK$^+$ ALCL, in whom outcomes can be favorable even when they are treated with cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP).[2] The International T-cell Lymphoma Project described outcomes for 340 patients with PTCL-NOS: 5-year overall survival (OS) and failure-free survival (FFS) were 32% and 20% respectively, with no clear benefit for patients treated with anthracyclines.[3] Despite these data, CHOP remains the most common induction therapy used. Attempts to improve on CHOP with intensive induction such as VIP/ABVD (etoposide/ifosfamide/cisplatin–doxorubicin/bleomycin/ vinblastine/dacarbazine) and other high-

dose sequential chemotherapy regimens have been mostly unsuccessful.[4-6] In one retrospective study, Hyper-CVAD/MA (hyper-fractionated cyclophosphamide/doxorubicin/vincristine/dexamethasone alternating with methotrexate/cytarabine) showed higher overall response rate (ORR) and progression-free survival (PFS), but not higher OS, than CHOP,[7] although this finding has not been replicated in other retrospective studies.[5] Given the substantially greater toxicity associated with this regimen, we recommend that Hyper-CVAD be used with caution.

The German High-Grade Lymphoma Study Group (DSHNHL) retrospectively analyzed the outcomes of patients with PTCL who were treated in prospective studies using CHOP-like regimens to address whether (1) shortening the interval from 21 to 14 days, or (2) adding etoposide to CHOP (CHOEP) affected outcomes.[8] In a subgroup analysis, patients age 60 or older with normal serum lactate dehydrogenase (LDH) levels achieved superior event-free survival (EFS) when treated with etoposide-containing regimens; this was largely the result of a significant benefit in patients with ALK$^+$ ALCL (3-year EFS 92% for CHOEP vs. 57% for CHOP; p = 0.012) whereas those with other histologies displayed a nonsignificant trend toward improvement (3-year EFS 61% for CHOEP vs. 48% for CHOP; p = 0.057).[8] The benefit of etoposide in younger patients was supported by a recent large Swedish registry analysis, which found that use of CHOEP (vs. CHOP) was associated with improved PFS in patients younger than 60.[9]

UP-FRONT TRANSPLANTATION IN PTCL

Because of the poor outcomes described using chemotherapy alone, up-front consolidation using high-dose chemotherapy

FIGURE 1. WHO 2008 Classification of Mature T-Cell Neoplasms According to Typical Presentation

mature T-cell and NK-cell neoplasms

nodal

Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma, ALK positive
Anaplastic large cell lymphoma, ALK negative

extranodal

Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma (subtype only)

leukemic

T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Aggressive NK-cell leukemia
Adult T-cell leukemia/lymphoma

cutaneous

Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30-positive T-cell lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Primary cutaneous peripheral T-cell lymphomas, rare subtypes Primary cutaneous gamma-delta T-cell lymphoma
Primary cutaneous CD8 aggressive epidermotropic T-cell lymphoma
Primary cutaneous CD4 small/medium T-cell lymphoma

and autologous stem cell transplantation (ASCT) in patients who achieve a response has been explored. The ORR following induction ranged from 66% to 82%, 41% to 72% of patients received ASCT, and the median OS was 3 to 5 years.[6,10-14] Reimer et al treated 83 patients (32 with PTCL-NOS) with CHOP induction followed by cyclophosphamide-total body irradiation conditioning and ASCT. At a median follow-up of 33 months, the 3-year PFS and OS were 36% and 48% respectively.[13] The Nordic Lymphoma Group treated 160 patients with PTCL (excluding ALK$^+$ ALCL) with bi-weekly CHOP with etoposide (CHOEP-14).[11] At a median follow-up of 60.5 months, the 5-year PFS and OS were 44% and 51% respectively, with marginal improvement in PFS (p = 0.04) and OS (p = 0.03) among patients with ALK$^-$ ALCL compared with other PTCL subtypes. In both studies, patients who had transplants had markedly superior outcomes compared with those who did not; however, the latter group consisted mostly of patients whose disease did not re-

spond to induction therapy or had comorbidities precluding SCT. The U.S. multicenter consortium reported that outside of clinical trials, only 33/341 patients (10%) treated at large academic centers received ASCT in first remission; this was associated with improvement in both PFS (hazard ratio [HR] 0.48; 95% CI, 0.27 to 0.84, p = 0.01) and OS (HR 0.48, 95% CI, 0.24 to 0.98, p = 0.04), although the typical limitations of a retrospective study apply.[7] Smith et al analyzed data collected by the Center for International Blood and Bone Marrow Transplant Research (CIBMTR) for 241 patients with mature T-cell lymphomas who underwent transplantation.[15] Patients in complete response (CR)1 had favorable outcomes (3-year PFS and OS of 58% and 70% respectively), indicating a major role for ASCT in patients with PTCL (other than those with primary cutaneous or ALK$^+$ ALCL) who are in first remission. However, it should be noted that no prospective randomized data demonstrating a clear advantage for transplant over induction chemotherapy alone currently exist.

Up-front allogeneic stem cell transplantation (alloSCT) has been explored in a prospective phase II study in which Corradini et al randomly assigned patients age 60 or older whose disease responded to induction therapy to either ASCT (14 patients) or alloSCT (23 patients) based on donor availability.[10] The reported 4-year OS (92% vs. 69%, p = 0.10) and PFS (70% vs. 69%, p = 0.92) were not significantly different; however, the study was neither designed nor powered for this comparison. The CIBMTR multicenter retrospective study attempted to compare outcomes for 115 patients who received ASCT and 126 who received alloSCT; patients in the alloSCT group were younger, but had more unfavorable features. The 3-year PFS for ASCT versus alloSCT in this analysis was 47% versus 33%, but only 17% of the patients who received ASCT and 14% of those with alloSCT had received just one prior line of treatment.[15] Thus, whether alloSCT as front-line consolidation offers additional disease control over ASCT remains controversial and is being addressed by

KEY POINTS

- Outcomes for patients with peripheral T-cell lymphoma treated with cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP)-like induction regimens with and without front-line consolidative stem cell transplantation will be summarized.
- Clinical data supporting the regulatory approval of pralatrexate, romidepsin, brentuximab vedotin, and belinostat for patients with relapsed/refractory disease will be reviewed.
- Trials combining these novel agents in combination with CHOP-like chemotherapy in previously untreated patients will be outlined.
- Studies using combinations of new agents in biologic doublets as salvage regimens will be described.
- Emerging clinical data on agents with promising clinical efficacy in phase I studies will be highlighted.

an ongoing German cooperative group study (EudraCT number: 2007-001052-39).

NEW AGENTS FOR RELAPSED AND REFRACTORY DISEASE

When treated using conventional chemotherapy alone, the outcome of patients with relapsed or refractory PTCL is particularly poor—a population-based registry study from the British Columbia Cancer Agency found that the median OS of patients with PTCL was only 5.5 months.[16] When used as a single agent in pretreated patients, bendamustine results in an ORR of approximately 50% with a median duration of response (DOR) of 3.5 months.[17] Gemcitabine has a similar ORR and the responses appear more durable.[18,19] However, there is a substantial unmet need for more options for patients whose disease does not respond to these therapies. Fortunately, several agents with novel mechanisms of action have been approved for this setting in the last 5 years, with several others undergoing evaluation in trials for potential future approval (Table 1).

Pralatrexate

Folates are critical for DNA synthesis and folate antagonism was one of the earliest successful chemotherapeutic pathways.[20] Pralatrexate is an inhibitor of dihydrofolate reductase that was designed to have increased affinity for the reduced folate carrier and therefore accumulates within cells and exhibits increased potency compared with methotrexate.[21] A phase I study demonstrated promising activity in T-cell lymphomas,[22] prompting an international phase II study (PROPEL). In this trial, 111 patients with relapsed or refractory aggressive PTCL were treated with single-agent pralatrexate (30 mg/m² administered intravenously once weekly),

achieving an ORR of 29% (CR 11%) with median DOR of 10.1 months.[23] The major toxicities seen with this agent are cytopenias (particularly thrombocytopenia, which may be dose limiting) and mucositis (any grade, 70%; grade ≥3, 22%), although there are data suggesting that prophylactic use of leucovorin may ameliorate the latter without compromising efficacy.[24] On the basis of this study, in 2009 pralatrexate gained U.S. Food and Drug Administration (FDA) approval for patients with PTCL who have received one or more systemic therapies.

Histone Deacetylase Inhibitors

Epigenetic therapies are useful for a range of hematologic malignancies, particularly PTCL. Recent publications have shown that histone deacetylase (HDAC) inhibitors have pleiotropic downstream effects including apoptosis, senescence, immune suppression, and angiogenesis.[25] HDACs are a group of enzymes with both histone and nonhistone targets that together govern chromatin conformation and gene expression.[26] Several agents in this class are effective in PTCL.

Romidepsin. Romidepsin is a cyclic, class 1-selective HDAC inhibitor that has been used as monotherapy for relapsed or refractory PTCL in two phase II studies.[27,28] Coiffier et al reported the larger study, in which 130 patients (53% PTCL-NOS) with a median of two prior treatments received 14 mg/m² romidepsin intravenously once weekly for 3 of 4 weeks.[28] Responses occurred at a median of 1.8 months; the ORR of 25% (CR 15%) was comparable across major histologic subtypes. Responses were durable, and a recent update of this study reported a median DOR of 28 months.[29] The most common toxicities included fatigue, thrombocytopenia, and gastrointestinal (GI) disturbance. Early reports suggesting prolongation of corrected QT interval were sub-

TABLE 1. Summary of Selected Novel Agents Currently Being Evaluated for Efficacy in Peripheral T-Cell Lymphoma

Agent	Mechanism	Phase	n	Grade ≥3 Toxicities	ORR	CRR	DOR
FDA-approved agents for PTCL							
Pralatrexate[23]	Folate antagonist	II	111	Mucositis	29%	11%	10.3 mo
Romidepsin[27,28]	HDAC inhibitor	II	47	Nausea, fatigue, thrombocytopenia	38%	17%	8.9 mo
		II	130	Thrombocytopenia, neutropenia, infection	25%	15%	28 mo*
Brentuximab vedotin[38]	Antibody-drug conjugate	II	35	Neutropenia, peripheral neuropathy	41%	24%	7.6 mo
Belinostat[31]	HDAC inhibitor	II	129	Hematologic	26%	10%	13.6 mo
Agents under investigation in PTCL							
Mogamulizumab[43]	Anti-CCR4 mAb	II	37	Neutropenia, rash	34%	17%	8.2 mo**
Alisertib (MLN8237)[54]	Aurora A kinase inhibitor	II	37	Hematologic, febrile neutropenia	24%	5%	NR
Duvelisib (IPI145)[69]	PI3Kγδ inhibitor	I	33	Transaminitis, rash, neutropenia	47%	12%	NR
Crizotinib[89]	ALK inhibitor	II	14	Diarrhea, vomiting, visual impairment	60%	36%	8.3 mo
Nivolumab[88]	Anti-PD1 mAb	I	5	Pneumonitis, rash, sepsis	40%	0%	NR

Abbreviations: ORR, objective response rate; CRR, complete response rate; DOR, duration of response; PI3K, phosphoinositide-3-kinase; CCR4, chemokine receptor-4; HDAC, histone deacetylase; ALK, anaplastic lymphoma kinase; NR, not reported; PD-1, programmed cell death-1; mAb, monoclonal antibody.
Response rates refer to patients with nodal PTCL subtypes where information available.
*Duration of response reported from updated report.[29]
**Median progression-free survival of patients with PTCL achieving response.

sequently attributed to antiemetic therapy and clinically significant dysrhythmias were not seen. Romidepsin gained FDA approval in 2011 for patients with PTCL who have at least one prior systemic therapy. Chihara et al reported a single-center phase I study to determine the safety profile of romidepsin administered on days 1 and 4 with ifosfamide/carboplatin/etoposide (ICE), with the hope that this combination would improve the CR rate over ICE alone and thus facilitate a greater proportion of patients receiving SCT.[30] The main toxicities were hematologic, with reversible grade 3 or greater thrombocytopenia in 87% of patients, and 5/7 (71%) response-evaluable patients achieved CR. This encouraging preliminary observation requires further confirmation in an expanded cohort and enrollment is ongoing.

Belinostat. Belinostat is a pan-HDAC inhibitor derived from hydroxamic acid that was evaluated in a single-arm phase II study with a dosing schedule of 1,000 mg/m^2 for days 1 through 5 in a 3-week cycle until progression or unacceptable toxicity.[31] Among 120 patients with PTCL confirmed by central pathology review, the ORR was 26% (CR 10%). As with romidepsin, responses were rapid (median time to response 5.6 weeks) and the median DOR was 8.3 months at the time of initial reporting. The major toxicities were hematologic (grade ≥3 anemia, neutropenia, and thrombocytopenia in 10, 13, and 13%, respectively).[31] Of note, belinostat appears to induce grade 3 or greater thrombocytopenia less frequently than romidepsin. On the basis of this study, in 2014 belinostat received accelerated FDA approval for patients with relapsed/refractory PTCL.

Brentuximab Vedotin

Although "naked" monoclonal antibodies (mAbs) against CD30 showed preclinical promise, clinical activity in patients with CD30$^+$ lymphomas was disappointing.[32] Brentuximab vedotin (BV) was designed to improve efficacy by conjugating the anti-CD30 mAb to the antimicrotubule agent monomethylauristatin E (MMAE). Binding to CD30 on the cell surface results in proteolytic release, internalization, and lysosomal uptake of MMAE, and tubule disruption, cell cycle arrest, and apoptosis.[33] ALCL has uniform strong CD30 expression, and on the basis of positive data from BV phase I trials,[34,35] a multicenter phase II study in patients with relapsed/refractory systemic ALCL (ALK-positive and -negative) was conducted.[36] Fifty-eight patients with a median number of two prior treatments were treated with 1.8 mg/kg BV intravenously every 3 weeks for up to 16 doses. The ORR was 86% (CR 57%) with 97% of patients having a reduction in tumor volume; responses occurred after a median of 6 weeks and the median DOR was 12.3 months. The most common toxicities were nausea, fatigue, GI disturbance, rash, and neutropenia (mostly grade 1 to 2). Peripheral sensory neuropathy was mainly grade 1 (all grades, 41%; grade 3, 12%) and was manageable with dose reductions and delays. Rare but potentially fatal adverse events reported include posterior multifocal leukoencephalopathy and pancreatitis.[37] Horwitz et al treated 35 patients with non-ALCL

PTCL subtypes (which have variable CD30 expression) using a similar study design.[38] The patients included in this study had either AITL (13 patients) or PTCL-NOS (22 patients); among these two histologic subtypes the ORR was 54% and 33% and the CR was 38% and 14%, respectively. Interestingly, CD30 expression by immunohistochemistry did not correlate with clinical outcomes, thus it could be hypothesized that MMAE diffuses out of the apoptotic tumor cell and exerts local effects on the tumor microenvironment. BV was approved by the FDA in 2011 for patients with systemic ALCL having failed at least one prior systemic therapy, and at the time of writing has National Comprehensive Cancer Network compendium class 2A listing for the treatment of patients with relapsed non-ALCL CD30$^+$ PTCL.

Alemtuzumab

CD52 is a pan-lymphoid antigen with variable expression in PTCL.[39] The anti-CD52 mAb alemtuzumab was used as a single agent in two small European studies in patients with pretreated PTCL.[40,41] Enblad et al treated 14 patients with 30 mg alemtuzumab administered intravenously three times weekly for up to 12 weeks.[40] Despite chemoprophylaxis with trimethoprim/sulfamethoxazole and valaciclovir, fatal opportunistic infections occurred in 5/14 (35%) patients, resulting in early study termination. The observed ORR was 36%. Interestingly, Zinzani et al showed that a reduced dose (10 mg) and a shorter schedule was better tolerated and effective, with an ORR of 50% in six patients with PTCL.[41] However, the toxic deaths that occurred in the first study have dampened enthusiasm for further development in patients with pretreated PTCL.

Mogamulizumab

Mogamulizumab, a defucoslyated mAb against chemokine receptor-4 (CCR4), was found to have single-agent activity in patients with relapsed/refractory T-cell lymphomas in a phase I study.[42] Ogura et al performed a phase II study in Japanese patients with relapsed/refractory T-cell lymphoma with 1.0 mg/kg mogamulizumab administered intravenously weekly for 8 weeks.[43] Among 37 patients treated, the median number of prior therapies was two and the main histologic subtypes were PTCL-NOS (16 patients), AITL (12 patients), and CTCL (8 patients). The ORR was 35% (CR 13%), with a median PFS of 3.0 months. The main toxicities reported were neutropenia (any grade, 38%; grade ≥3, 19%), fever (grade 1–2, 30%), infusion reaction (grade 1–2, 24%), and skin disorders (any grade, 51%; grade ≥3, 11%). Although CCR4 expression by immunohistochemistry was required for study entry, there was little correlation between expression of target antigen and response, similar to the data for BV and CD30. The authors hypothesized depletion of CCR4$^+$ regulatory T (T$_{reg}$) cells, resulting in an increase in the number of CD8$^+$ cytotoxic T-cells, as a mechanism of tumor control, and on the basis of these data mogamulizumab gained approval for the treatment of relapsed PTCL in Japan in 2014. Zinzani et al performed a multicenter European phase II study with 38 patients and reported a lower ORR of 11% with

a similar median PFS of 2 months,[44] although the limited DOR suggests that mogamulizumab might be best suited for combination studies. However, one possible exception may be the highly aggressive and chemorefractory disease adult T-cell lymphoma/leukemia. Ishida et al performed a phase II study of mogamulizumab in 28 patients with relapsed/refractory disease, in which the ORR was 50% with median PFS and OS of 5.2 and 13.7 months respectively.[45]

Lenalidomide

The immunomodulatory drug lenalidomide has substantial activity in myeloma and B-cell lymphomas.[46,47] Three small studies have explored lenalidomide (25 mg administered orally for days 1 to 21 of a 28-day cycle) in patients with relapsed/refractory PTCL, with a reported ORR of 22% to 39% (CR 8% to 30%).[48-50] Although the median DOR in the largest study of 54 patients was only 3.6 months, there was a nonsignificant trend toward higher response rates among the subset of patients with AITL.[48]

Alisertib

Aurora A kinase regulates mitotic entry and spindle formation; it is overexpressed in aggressive lymphomas and has a potential role in oncogenesis.[51] The orally available, small-molecule competitive inhibitor alisertib induces cytotoxicity in a range of solid and hematologic tumors.[52] Friedberg et al performed a multicenter phase II study of alisertib in 48 patients with heavily pretreated aggressive lymphomas.[53] Although the ORR was 27% overall, it was 4/8 (50%) among patients with T-cell lymphoma, with 3/4 (75%) maintaining a response for more than 1 year at the time of reporting. Subsequently, the SWOG1108 phase II study extended this observation in an additional 37 heavily pretreated patients with a range of PTCL subtypes.[54] Alisertib was administered at a dosage of 50 mg twice daily for 7 days in a 21-day cycle. The most common adverse events (AEs) of grade 3 or greater

were hematologic, observed in approximately one-third of patients; febrile neutropenia was seen in 14%. The ORR was 24% overall and 31% in patients with PTCL-NOS. As a pathway to potential approval, an ongoing international phase III registration study is comparing alisertib to investigators choice (gemcitabine, pralatrexate, or romidepsin) in patients with PCTL (NCT01482962).

MOVING NOVEL AGENTS INTO THE FRONT LINE

With many drugs demonstrating efficacy in relapsed/refractory PTCL, integrating agents into front-line therapy is a major focus of drug development efforts. The conventional approach has been to be combine novel agents with chemotherapy in an attempt to discover an "R-CHOP" equivalent for PTCL; a summary of these studies is provided in Table 2.

CHOP/CHP Plus Brentuximab Vedotin

Because of the promising single-agent activity of brentuximab, a phase I study of CHOP without vincristine (CHP) and with brentuximab was designed to minimize the overlapping toxicity of peripheral sensory neuropathy. This study enrolled 39 patients with CD30$^+$ PTCL, although most (32 patients) had ALCL.[55] Two schedules of administration were used: BV×2 followed by CHOP×6 (sequential, 13 patients) or BV given concurrently with CHP (combination, 26 patients). The sequential arm was closed by the sponsor after two patients who responded to BV progressed during CHOP. Toxicity was similar between the schedules and manageable; the most common AE overall was peripheral neuropathy (31% with grade ≥3 in the combination group), followed by hematologic febrile neutropenia (21% in the combination group), fatigue, nausea, and GI disturbance. The combination was highly active, with an ORR of 85% and 100% (CR, 62% and 88%) and 1-year PFS of 77% and 71% in the sequential and combination groups, respectively, and none of these

TABLE 2. Summary of Selected Chemotherapy/Novel Agent Combinations for Untreated Peripheral T-Cell Lymphoma

Combination	Study Group	Major Histologies	Phase	n	ORR	CRR	PFS	OS
CHOP + romidepsin[57]	LYSARC	NR	Ib/II	35	68%	51%	18 mo 57%	18 mo 76%
CHOP + vorinostat[60]	MDACC	PTCL-NOS 5, AITL 5, ALCL 4	I	14	93%	93%	2 yr 79%	2 yr 81%
CHOP-14 + alemtuzumab[62]	GITIL	PTCL-NOS 14, AITL 6, ALCL 3	II	24	75%	71%	2 yr 48%	2 yr 53%
CHOP + alemtuzumab[63]	HOVON	PTCL-NOS 10, AITL 6	II	20	90%	60%	2 yr 27%*	2 yr 55%
CHO(E)P + alemtuzumab[61]	DSHNHL	PTCL-NOS 21, AITL 11, ALCL 4	II	41	61%	58%	3 yr 32%	3 yr 62%
CHP + brentuximab vedotin[55]	U.S./European multicenter	ALCL 32, PTCL-NOS 2, ATLL 2, AITL 2	I	39	100%**	88%**	1 yr 71%**	1 yr 88%**
CEOP + pralatrexate[56]	T-cell consortium	PTCL-NOS 21, AITL 8, ALCL 4	II	33	70%	45%	1 yr 48%^	1 yr 80%
CHOP + denileukin diffitox[99]	U.S. multicenter	PTCL-NOS 19, AITL 10, ALCL 8	II	49	65%	50%	2 yr 43%	2 yr 65%
CHOP + bortezomib[74]	CISL	PTCL-NOS 16, ENKTL 10, AITL 8	II	46	76%	65%	3 yr 35%	3 yr 47%

Abbreviations: ORR, objective response rate; CRR, complete response rate; DOR, duration of response; NR, not reported; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; ICE, ifosfamide/carboplatin/etoposide; CHP, cyclophosphamide/doxorubicin/prednisone; CEOP, cyclophosphamide/etoposide/doxorubicin, prednisone; CHOEP, cyclophosphamide, doxorubicin, vincristine/etoposide/prednisone; LYSARC, Lymphoma Academic Research Organization; MDACC, MD Anderson Cancer Center; GITIL, Italian Group for Innovative Lymphoma Therapies; HOVON, Dutch-Belgian Haemato-Oncology Group; CISL, Consortium for Improving the Survival of Lymphoma; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ATLL, adult T-cell leukemia/lymphoma; ENKTL, extranodal NK/T-cell lymphoma.
*Event-free survival.
**Results for combination CHP + brentuximab arm.

patients underwent front-line consolidative ASCT.[55] The combination schedule is currently being compared with CHOP for patients with CD30$^+$ PTCL in the phase III ECHELON-2 study (NCT01777152).

CEOP Plus Pralatrexate

Advani et al reported preliminary results from the T-cell consortium trial of CEOP (cyclophosphamide/etoposide/vincristine/prednisone) alternating with pralatrexate in newly diagnosed patients with PTCL.[56] Etoposide was substituted for doxorubicin because of data suggesting improved efficacy (discussed above) and the lack of proven benefit for anthracyclines. CEOP was administered in the standard fashion, with pralatrexate administered at 30 mg/m^2 intravenously on days 15, 22, 29; up to 6 cycles in total were planned and growth factor support was mandatory. The goal was to improve the CR rate to facilitate optional ASCT, which was allowed at the investigator's discretion. The ORR was 70% (CR 45%) and the 1-year EFS was 48%. Observed toxicities of grade 3 or greater included hematologic events, sepsis, and mucositis.

CHOEP Plus HDAC Inhibitors

The French cooperative group LYSARC (Lymphoma Academic Research Organization) performed a phase Ib/II study of CHOP with romidepsin in 35 patients with treatment-naive PTCL. CHOP21×8 was given at standard doses, with the dose of romidepsin escalated (phase II dose 12 mg/m^2 on days 1 and 8 in a 21-day cycle). The major adverse events were, predictably, hematologic: grade 3 or greater neutropenia (38%), thrombocytopenia (19%), and anemia (9%). The ORR was 68% (CR 51%) and the estimated PFS at 18 months was 57%.[57] This combination is being tested in a randomized phase III study (NCT01796002). The Italian Cooperative Group is performing an ongoing phase I/II study of romidepsin in combination with CHOEP followed by ASCT (NCT02223208). Because of its activity in cutaneous T-cell lymphoma,[58,59] Oki et al. tested the combination of the orally available pan-HDAC inhibitor vorinostat with CHOP in a small phase I study of 14 newly diagnosed patients with PTCL.[60] Toxicities were comparable to those expected from standard CHOP, with the exception of mild diarrhea in approximately half of all patients treated. All 12 patients who completed therapy achieved a CR (93% of total population) suggesting that this promising combination warrants further evaluation. A multicenter phase I study evaluating the combination of CHOP with belinostat is in progress (NCT01839097).

CHOP Plus Alemtuzumab

Alemtuzumab has also been explored in combination with CHOP-like therapy in three separate phase II multicenter European studies with markedly different treatment schedules.[61-63] The Italian study used 8 doses of CHOP-14 with 30 mg alemtuzumab given intravenously at 2-week intervals (total 240 mg)[62]; the HOVON (Dutch-Belgian Hemato-Oncology Group) study also used CHOP-14, but intensified alemtuzumab with three 30-mg doses per cycle (total 720 mg)[63]; the DSHNHL study used alemtuzumab (133 mg over 4 weeks) as consolidation following CHOP induction (with etoposide for patients older than 60) in 41 patients with newly diagnosed PTCL.[61] In all three studies, serious opportunistic infectious complications such as CMV reactivation, disseminated zoster and tuberculosis JC virus encephalitis, invasive fungal infections, and EBV-associated lymphoproliferative disease were observed despite aggressive chemoprophylaxis. Although comparisons between small phase II studies in heterogeneous disease groups are difficult, it appeared that both the ORR and rate of infection of grade 3 or greater were proportional to the cumulative dose of alemtuzumab administered. The ongoing ACT-1 (NCT00646854) and ACT-2 (EudraCT 2007-000821-23) phase III studies are randomized comparisons of CHOP ± alemtuzumab in PTCL in younger (with ASCT consolidation) and older patients respectively.

BIOLOGIC DOUBLETS IN THE RELAPSED SETTING

Moving beyond the traditional "CHOP+X" development pathway are a plethora of studies testing combinations of novel agents and eschewing chemotherapy altogether. At present, these biologic doublets are mostly being tested in the relapsed/refractory setting. A selection of such studies is presented in Table 3. We anticipate that the most promising combinations will be investigated in chemotherapy-free front-line protocols, as is currently underway in B-cell lymphoma. At the present time, results from most of these protocols are not mature. Hopfinger et al explored the combination of lenalidomide, vorinostat (400 mg daily, fixed dose), and dexamethasone in a phase I/II study and found that the maximum tolerated dose (MTD) of lenalidomide in the combination was only 5 mg daily.[64] Planned dose escalation was aborted because of grade 3 thrombocytopenia and stroke at the 10-mg dose of lenalidomide. Probably because of the low tolerated dose of lenalidomide, activity was modest (ORR 25%, median PFS 2.2 months). Tan et al recently reported on a phase II study of the HDAC inhibitor panobinostat with the proteasome inhibitor bortezomib in patients with pretreated PTCL.[65] The main toxicities were hematologic, diarrhea, fatigue, and peripheral sensory neuropathy; among 23 evaluable patients, the ORR was 43% (CR 22%) with five patients successfully bridged to allogeneic stem cell transplantation.

Several combination studies are underway using romidepsin in combination with other biologic agents. There are preclinical data suggesting potent synergism between romidepsin and alisertib in T-cell lymphomas,[66] an observation supported by preliminary results from a phase I study of the combination being performed at The University of Texas MD Anderson Cancer Center.[67] Among the included histologies, activity seems most promising in PTCL, with a CR observed at the lowest dose level and ORR of 1/3 (33%). This study is ongoing and the expansion cohort will be restricted to patients with PTCL. Romidepsin is also being explored in combination with several other nonchemotherapic agents, including lenalidomide, 5-azacitidine, and pralatrexate, with promising early results. Preliminary results from a phase I/II

TABLE 3. Selected Ongoing Studies Testing Biologic Doublets in Peripheral T-Cell Lymphoma

Agents	Phase	Population	Sponsor/Site	ClinicalTrials.gov
Romidepsin + lenalidomide	I	Untreated PTCL	Northwestern University	NCT02232516
	I	RR lymphoma/myeloma	Yale/Peter MacCallum Cancer Centre	NCT01742793
	I	RR lymphoma/myeloma	Memorial Sloan Kettering Cancer Center	NCT01755975
Romidepsin + oral 5-azacitidine	I	RR lymphoid malignancies	Columbia University	NCT01998035
Romidepsin + alisertib[67]	I	RR aggressive NHL	National Cancer Institute MD Anderson Cancer Center	NCT01897012
Alisertib + vorinostat	I	RR lymphoma	National Cancer Institute	NCT01567709
Carflizomib + belinostat	I	RR NHL	Massachusetts General Hospital	NCT02142530
Carflizomib + vorinostat	I	RR lymphoma	University of Rochester	NCT01276717
Pralatrexate + romidepsin	I/II	RR lymphoid malignancies	Columbia University	NCT01947140
Bortezomib + romidepsin	I	RR indolent lymphoid malignancies	Virginia Commonwealth University	NCT00963274

Abbreviations: PTCL, peripheral T-cell lymphoma; NHL, non-Hodgkin lymphoma; RR, relapsed/refractory.

combination of romidepsin/lenalidomide suggested that the combination is active, with ORR in relapsed PTCL of 58% but only 1 of 12 patients entering into CR.[68] Phase II studies are planned and Petrich et al will be conducting a front-line PTCL phase II trial of romidepsin plus lenalidomide. As these biologic doublets move into the front-line setting further information will be gained in terms of their efficacy, although challenges remain with respect to which components of efficacy (ORR, CR, or PFS) are most important to determine which biologic regimens should be selected for front-line randomized comparative trials against standard chemotherapy regimens such as CHOP or CHOEP.

AGENTS IN EARLY CLINICAL DEVELOPMENT
PI3K Inhibitors
The orally administered phosphoinositide-3-kinase (PI3K) gamma/delta inhibitor duvelisib (IPI-145) was assessed in a phase I study of 33 heavily pretreated patients with T-cell lymphoma (CTCL 17, PTCL 16).[69] Most patients were treated at the MTD of 75 mg twice daily; among patients with PTCL the ORR was 47% (CR 12%) with a favorable toxicity profile (the most common AEs were transaminitis, rash, and neutropenia). These highly promising results warrant further evaluation. Based on preclinical data,[70] another PI3K gamma/delta inhibitor, RP-6530, is currently being evaluated in a phase I study of patients with relapsed/refractory lymphomas and appears to be well tolerated, although no patients with PTCL were included in the preliminary report.[71] Another interesting approach to improve the efficacy of novel therapeutics is the design of bifunctional molecules through medicinal chemistry. One such agent, CUDC-907, is both a pan-HDAC and PI3K inhibitor and has shown greater preclinical activity than single-agent HDAC or PI3K inhibitors.[72] The compound is currently in a phase I clinical trial of refractory lymphoid malignancies (NCT01742988).

Proteasome Inhibitors
The first agent in this class, bortezomib, had moderate activity as a single agent in CTCL[73] and in combination with

CHOP in untreated patients with PTCL.[74] The second-generation proteasome inhibitor carfilzomib is being investigated in an ongoing phase I study (NCT01336920).

IDH2 Inhibitors
Gain-of-function mutations in the genes encoding the metabolic enzymes isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) result in accumulation of R-2-hydroxyglutarate, a metabolite that induces epigenetic changes that drive oncogenesis.[75] Mutations in *IDH1* and *IDH2* have been reported in a range of hematologic and solid tumors, including 45% of cases of AITL.[76,77] AG-221 is a first-in-class, oral selective inhibitor of mutant IDH2 enzyme that appears to be well tolerated, with promising activity and durable responses in a preliminary report of a phase I study in advanced IDH2-positive hematologic malignancies.[78] It is being evaluated in a phase I/II study including patients with IDH2-positive AITL (NCT02273739).

Retinoids
Vitamin A derivatives have demonstrated a range of anticancer functions including antiangiogenesis activity and induction of apoptosis and differentiation.[79] With the exception of acute promyelocytic leukemia, their clinical development has been limited by their toxicity profile. The synthetic retinoic acid (fenretinide) appears to be better tolerated than all-trans retinoic acid, and a phase I study using a pharmacologically optimized emulsion formulation resulted in a clinical benefit rate (CR+PR+SD) of 64% among 11 patients with relapsed T-cell lymphomas.[80]

Selective Inhibitors of Nuclear Export
Selinexor (KPT-330) is a first-in-class, selective, reversible inhibitor of nuclear export that binds to the nuclear export protein XPO1, forcing its nuclear retention and activation of tumor suppressor proteins.[81] It has shown preclinical activity in a range of malignancies.[82-84] Preliminary data from a phase I study in patients with relapsed/refractory hematologic malignancies suggest that it is well tolerated and has potential efficacy in T-cell lymphoma with one outcome of CR and two

of stable disease (SD) among three evaluable patients.[85] A phase II study in PTCL (and other histologies) is planned.

Immune Checkpoint Inhibitors

PD-1 is an immune checkpoint receptor that inhibits T-cell activation upon binding to its ligand PD-L1, which is over-expressed in many lymphoid malignancies. Antibodies specific for PD-1, such as nivolumab, thus induce antitumor T-cell activation and are highly active in Hodgkin lymphoma.[86] PD-L1 is known to play an important role in the tumor microenvironment in PTCL, providing a preclinical rationale for PD-1 inhibitors in these conditions.[87] A phase I study in heavily pretreated patients with NHL including 23 patients with T-cell lymphoma recently reported a favorable toxicity profile and ORR of 17%. However, among patients with PTCL, the ORR was 2/5 (40%).[88]

ALK Inhibitors

For patients with ALK$^+$ ALCL, the *EML4-ALK* fusion onco-gene provides an attractive target. Crizotinib, the first-generation ALK inhibitor, was used in a phase Ib study of 15 patients with ALK$^+$ lymphomas (14 with ALK$^+$ ALCL).[89] The main toxicities were diarrhea, vomiting, and visual impairment; the ORR was 60%. This agent is being tested in a phase I/II study in combination with chemotherapy in untreated patients (NCT01979536) and in a study of relapsed/refractory ALK$^+$ ALCL (NCT00939770). As with many tyrosine kinase inhibitors, secondary resistance has been reported and second-generation agents such as ceritinib (LDK378) will undoubtedly be explored in patients who experience treatment failure.[90-93] A phase I study that includes an arm enrolling patients with ALK$^+$ malignancies other than lung cancer is in progress (NCT01283516).

TOWARD MOLECULAR STRATIFICATION IN PTCL

Gene expression profiling (GEP) has advanced our understanding of the classification,[92] prognostic stratification, and molecular pathogenesis of T-cell lymphomas. The Mayo group recently described two genetic subsets of ALK$^-$ ALCL with disparate clinical outcomes: patients with rearrangements in *DUSP22* (at the 6p25.3 locus, found in 30% of cases) had excellent outcomes, comparable to those of ALK$^+$ ALCL, whereas those with *TP63* rearrangement (on 3q28, seen in 8% cases) had dismal prognosis.[93] Several recurrent somatic mutations in genes such as *TET2*,[94] *IDH2*,[77] and *RHOA*[95,96] have been described, although their clinical relevance requires further investigation. In PTCL-NOS, a recurrent t(5;9)(q33;q22) translocation resulting in a *ITK-SYK* fusion gene and SYK overexpression was described in a subset of patients with follicular histology.[97] Finally, small nucleolar RNA (snoRNAs) have been shown to have potential diagnostic and prognostic significance in PTCL.[98] Further development and more widespread utilization of these technologies are clearly needed to deliver on the promise of true precision medicine for patients with T-cell lymphomas.

CONCLUSION

Cooperative studies in the last 5 years have successfully enabled the rapid completion of phase I/II studies and brought four new drugs for patients with T-cell lymphoma to the clinic. Continuing efforts are needed to complete confirmatory randomized phase III studies in combination with chemotherapy. The development of chemotherapy-free regimens using the most active biologic agents in PTCL will be a critical focus of research efforts in the future. Additional efforts to develop molecular targeted approaches are also clearly needed in order to rationally select a treatment plan that would be predicted to have the highest efficacy for a particular patient.

Disclosures of Potential Conflicts of Interest

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Novel Agents in the Therapy of Hodgkin Lymphoma

Stephen Ansell, MD, PhD

OVERVIEW

Hodgkin lymphoma (HL) is a B-cell malignancy that typically has a favorable prognosis when treated with chemotherapy, often in combination with radiation therapy. The prognosis for patients whose disease relapses or is refractory, however, is far less favorable and novel therapies are needed for these patients. The unique cellular composition of HL provides a number of opportunities to target either the malignant Reed-Sternberg cell or the inflammatory tumor microenvironment. Antibody-drug conjugates targeting CD30, small molecule inhibitors of cell signaling, and antibodies that inhibit immune checkpoints, have all demonstrated activity in HL. Current and future trials are exploring the use of these agents in combination with each other and with standard chemotherapy.

Hodgkin lymphoma is an uncommon B-cell malignancy affecting approximately 9,000 new patients each year and representing approximately 12% of all lymphomas seen in the United States.[1] HL is composed of two distinct disease entities, namely classical HL and nodular lymphocyte predominant HL. Classical HL is further subcategorized as nodular sclerosis, mix cellularity lymphocyte depletion, and lymphocyte rich HL.[2] Although HL commonly responds well to initial therapy and a substantial percentage of patients have durable remissions and many are cured, a subset of patients continue to experience relapsed disease, and patients progressing after intensive treatments, such as autologous stem cell transplantation, have a very poor outcome. In the recent past, particularly effective novel therapies have been identified to treat these patients, and these novel agents are now being integrated into earlier lines of treatment.

THERAPEUTIC TARGETS IN HODGKIN LYMPHOMA

HL has a unique histologic pattern in that a small fraction of the nodal infiltrate is attributable to malignant Reed-Sternberg cells.[3] A vast majority of the cells seen in the tumor tissue are reactive inflammatory cells, including a dense infiltrate of T cells, histiocytes, eosinophils, and plasma cells.[4] Furthermore, the tumor microenvironment is unique in that the activated cells secrete multiple chemokines and cytokines, which attract many of these cells to the tumor environment. These cytokines and immunologically active molecules include thymus- and activation-regulated chemokine (TARC/CCL17), interleukin (IL)-6, IL-13, and soluble IL-2 receptor.[5,6] The immune cells attracted to the tumor microenvironment appear to support the growth of Reed-Sternberg cells by secreting additional survival factors. The

immune effector cells present in the tumor, however, appear unable to mount an effective antitumor immune response. Initially, this was attributed to the fact that the T cells present in the tumor were predominantly T helper 2 (TH2) cells. Recent data, however, have suggested they may well be TH1 cells in view of the fact that TH1-associated *TBET* is abundant in classical HL and TH2-associated *GATA3* is expressed in substantially lower levels.[7]

An effective immunologic response, however, may be considerably suppressed as a result of signaling through programmed death (PD)-1. PD-1 is expressed on activated T cells, and signaling through PD-1 suppresses T-cell function. Malignant Reed-Sternberg cells express high levels of PD-1 ligands, namely PD-L1 and PD-L2. Expression of the PD-1 ligands on Reed-Sternberg cells is related to chromosomal translocations that result in amplification of the PD-L1 and PD-L2 loci on chromosome 9p24.1 and result in suppression of the antitumor immune response. Epstein-Barr virus infection, which is often seen in patients with HL, may also induce the expression of PD-1 ligands.[8] These mechanisms are responsible for upregulation of Janus kinases and signal transducers and activators of transcription (JAK-STAT) signaling; activation of JAK-STAT signaling and overexpression of PD-L1 appear to be higher among patients with multiple relapsed HL.

Other intratumoral factors associated with disease progression and a poorer outcome in HL include the presence of other intratumoral immune cells, as well as immune mechanisms in the peripheral blood. Tumor-associated macrophages, particularly increased numbers of CD163+ macrophages, have been associated with a poorer outcome and decreased overall survival.[9] Factors in the peripheral blood (including increased serum cytokines and the absolute lymphocyte to monocyte count ratio, which may reflect a patient's immune status) are

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associated with patient prognosis.[6,10] These features of an active tumor microenvironment and immune response represent a potential target for novel therapies.

Furthermore, the malignant Reed-Sternberg cells represent a therapeutic target in that they express CD30, a member of the tumor necrosis factor receptor family.[11,12] CD30 is not typically expressed on most human tissue under normal physiologic conditions. CD30 can, however, be expressed on thymocytes during thymus development, on pancreatic exocrine cells, and on cells in the uterus and endometrium during pregnancy. Activated T cells can also transiently up-regulate CD30. The limited expression of CD30 and the substantial expression of CD30 on Reed-Sternberg cells make CD30 a useful target for treatment in HL.

NOVEL AGENTS IN HODGKIN LYMPHOMA

Based on the unique composition of the tumor, new agents have been developed that either specifically target Reed-Sternberg cells, target the inflammatory infiltrate, or reverse the suppressed immune microenvironment. Many of these agents have demonstrated substantial clinical activity in patients with HL who have failed multiple previous lines of treatment.

Brentuximab Vedotin

Brentuximab vedotin, although not strictly a new agent, demonstrates the benefit of specifically targeting the Reed-Sternberg cell. Initial clinical trials utilizing this CD30-directed antibody-drug conjugate included large numbers of patients with HL. In an initial phase I trial, patients received brentuximab every 3 weeks. The trial confirmed that 17 patients with HL had objective responses (ORs) (11 patients had complete responses).[13] Of the 12 patients with HL who received treatment at the maximum tolerated dose, an OR rate of 50% was seen. These results were confirmed in a pivotal phase II trial using brentuximab vedotin in patients with relapsed and refractory HL, all of whom had previously been treated with an autologous stem cell transplant.[14] In a cohort of 102 patients, all of whom received brentuximab vedotin at a dose of 1.8 mg/kg every 3 weeks, the overall response rate (ORR) was 75%, with a complete response rate (CRR) of 34%. The median progression-free survival (PFS) for all patients in the study was 5.6 months; however, the median duration of response for patients obtaining a complete remission was 20.5 months. Long-term follow-up of this trial confirmed the durability of the responses.[15] Of the 34 patients who obtained complete remission, 16 (47%) remained progression free at a median of 53.3 months.

Based on these promising results, brentuximab vedotin subsequently has been incorporated into combination therapy. A clinical trial utilizing brentuximab vedotin in combination with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) or AVD (bleomycin omitted) chemotherapy found that the maximum tolerated dose of brentuximab vedotin in combination with the chemotherapy was defined as 1.2 mg/kg.[16] Importantly, however, the study found that when brentuximab vedotin was given with the bleomycin-containing regimen, it resulted in significant pulmonary toxicity. A subsequent cohort of patients treated with AVD chemotherapy tolerated the treatment far better with no additional pulmonary toxicity; the combination was highly effective, with CRs seen in 96% of the patients. Based on these promising results, a front-line randomized control trial of AVD chemotherapy plus brentuximab vedotin compared to standard ABVD chemotherapy is currently ongoing.

Everolimus

The phosphatidylinositide 3-kinase/mammalian target of rapamycin (PI3K/mTOR) signaling pathway has been shown to be activated in patients with HL. Everolimus is an oral antineoplastic agent that targets this pathway, specifically the mTOR complex 1 (mTORC1). Everolimus not only may target the signaling pathways within the Reed-Sternberg cells but may also suppress signaling within the immune infiltrate and production of cytokines present in the tumor microenvironment. A clinical trial of everolimus administered at a dose of 10 mg orally every day, was performed among 19 patients with relapsed and refractory HL.[17] The majority of patients had received multiple previous lines of therapy and 84% of the patients had undergone a previous autologous stem cell transplant. In this small cohort of patients the ORR was 47%, with one patient experiencing a complete remission and eight patients achieving partial remissions. The median time to disease progression was 7.2 months. Overall, the treatment was well tolerated and four of the responding patients remain progression free at 12 months. This study confirmed that everolimus has single-agent activity in patients with relapsed and refractory HL and confirmed that targeting the mTOR pathway in HL is clinically warranted.

Panobinostat and Mocetinostat

Agents that target acetylases may regulate several oncogenic pathways including cell cycle progression, cell survival, angiogenesis, and antitumor immunity. Panobinostat and mocetinostat target histone deacetylase, and these agents may be effective in patients with HL by modulating serum cytokine

levels and the expression of PD1 on intratumoral T cells. In one study, 129 patients with relapsed and refractory HL received 40 mg of panobinostat orally three times per week.[18] Treatment with panobinostat was effective as tumor reductions were seen in 74% of the patients, and ORs were achieved by 35 patients (27%). Thirty patients (23%) had partial responses to treatment and five patients (4%) had CRs. The median duration of response was 6.9 months, and the median PFS was 6.1 month. The agent was reasonably well tolerated, and serum testing for TARC showed reduction in TARC levels for patients responding to treatment.

Mocetinostat has also been tested in patients with relapsed and refractory classical HL.[19] In a clinical trial, 51 patients were treated at a dose level of either 110 mg or 85 mg. The group who received 110 mg had increased toxicity; 85 mg was felt to be a more optimal dose level. Among the 51 patients, two had CRs and 12 had PRs. Serum cytokines were also tested in each of the patients, and levels of multiple cytokines significantly decreased after treatment was initiated. TARC levels decreased by more than 40% between baseline and day 8 of treatment and correlated with clinical benefit.

JAK Inhibitors

JAKs are a family of intracellular non-receptor tyrosine kinases that transduce signals from cell surface receptors activated by cytokines and growth factors. After phosphorylation, JAKs lead to recruitment of STAT proteins. The STAT proteins subsequently translocate to the nucleus and trigger transcription of target genes involved in cell proliferation, cell survival, and immune response.

Aberrant activation of the JAK-STAT pathway has been linked to a variety of malignancies, including HL. SB1518 is a small molecule inhibitor of JAK2 kinase with preclinical activity in lymphoid malignancies. This JAK inhibitor has been tested in a phase I clinical trial of a variety of lymphomas, including refractory HL.[20] Doses of 100 to 600 mg/day were tested, and the drug was found to be well tolerated. Among the study's 34 patients, the ORR was 14%, including three partial remissions. In the group of patients with HL, however, none of the 14 patients had a partial remission or better. However, at least five of the patients with HL did benefit from the treatment, with a decrease in the sites of active disease.

Lenalidomide

Lenalidomide has a diverse set of possible mechanisms of action. It is proposed to directly induce cell death in malignant B cells and to indirectly regulate the tumor microenvironment. Lenalidomide has immunomodulatory and antiangiogenic properties and may specifically modulate many of the changes in the microenvironment, including the skewing of the cytokine profile, the altered immune cell infiltrate, and the recruitment of macrophages to the tumor microenvironment.

In view of the potential benefits to modulating the microenvironment by using lenalidomide, this agent has been tested in a clinical trial of relapsed and refractory classical HL.[21] In a study of 38 patients with classical HL, most of whom had previously been treated with an autologous stem cell transplant, patients received a standard dose of 25 mg daily for 3 out of every 4 weeks. Overall, the treatment was well tolerated, and of 36 evaluable patients, the study confirmed one complete remission and six partial remissions, resulting in an ORR of 19%. When patients who clinically benefited were included, a third of the patients benefited from treatment. Serum levels of cytokines were tested and plasma levels of CCL17 and CCL22 were associated with subsequent response. Lenalidomide was potentially beneficial in patients with refractory HL.

Anti-PD-1 Antibodies

The PD-1 pathway serves as an immune checkpoint to dampen immune responses. As outlined above, the tumor microenvironment in classical HL overexpresses the PD-1 ligands, resulting in a successful mechanism of tumor immune escape. Blocking PD-1 interactions with its ligands is therefore a promising treatment approach, particularly as genetic alterations result in PD-L1 and PD-L2 copy gain and thus overexpression of PD-1 ligands. As mentioned above, Epstein-Barr virus infection is a further mechanism that upregulates PD-1 ligand expression. Two recent clinical trials targeting PD-1/PD-1-ligand interactions have been reported, both with remarkable clinical results. In a clinical trial utilizing nivolumab, 23 patients with relapsed or refractory HL were treated every 2 weeks with 3 mg/kg of the antibody.[22] The majority of these patients had previously received an autologous stem cell transplant, and most had received previous brentuximab vedotin. In this group of patients, an ORR of 87% (20 out of 23) patients was seen, with a CRR of 17% and a PR rate of 70%. The PFS at 24 weeks was 86% and 11 of the patients continued on therapy, suggesting that the responses were durable.

In a second clinical trial utilizing the anti-PD-1 monoclonal antibody pembrolizumab (MK-3475), patients received the drug at a dose of 10 mg/kg administered every 2 weeks.[23] In this group of very heavily previously treated patients, pembrolizumab was well tolerated and similar dramatic clinical responses were seen. The ORR was 53%, with three patients (20%) having a complete remission and five additional patients (33%) having a partial remission. Virtually all patients appeared to have benefitted from therapy and the responses also appeared durable.

CONCLUSIONS AND FUTURE DIRECTIONS

The results presented above show that multiple agents have substantial activity in relapsed and refractory HL. These agents have all been tested as single agents, and therefore an important future approach will be to combine these agents with each other as well as with standard chemotherapy approaches. These future studies will specifically need to exclude the possibility of overlapping toxicities. However, provided the treatments can be safely given together, the future of patients with HL may be markedly improved as these agents move into earlier lines of treatment.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked "L" indicate leadership positions. Relationships marked "I" are those held by an immediate family member; those marked "B" are held by the author and an immediate family member. Institutional relationships are marked "Inst." Relationships marked "U" are uncompensated.

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LYMPHOMA AND PLASMA CELL DISORDERS

Personalized Therapy for Multiple Myeloma in a Value-Oriented Environment

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Smoldering Multiple Myeloma: When to Observe and When to Treat?

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OVERVIEW

Smoldering multiple myeloma (SMM) is an asymptomatic disorder characterized by the presence of at least 3 g/dL of serum M-protein and/or 10% to 60% bone marrow plasma cell infiltration with no myeloma-defining event. The risk of progression to active multiple myeloma (MM) is not uniform and several markers are useful for identifying patients at high risk of progression. The definition of the disease has recently been revisited and patients with asymptomatic MM at 80% to 90% of progression risk at 2 years are now considered to have MM. Although the current standard of care is not to treat, a randomized trial in patients with high-risk SMM that compared early treatment versus observation demonstrated that early intervention resulted in substantial benefits in terms of time to progression and overall survival (OS). These findings highlight the need to follow a correct diagnosis by an accurate risk stratification to plan an optimized follow-up according to the risk of disease progression.

Smoldering multiple myeloma is an asymptomatic plasma cell disorder defined in 1980 by Kyle and Greipp on the basis of a series of six patients who met the criteria for MM but whose disease did not have an aggressive course.[1]

At the end of 2014, the International Myeloma Working Group (IMWG) updated the definition of SMM as a plasma cell disorder characterized by a minimum of 3 g/dL of serum M-protein and/or 10% to 60% bone marrow plasma cells (BMPCs), but with no evidence of myeloma-related symptomatology (hypercalcemia, renal insufficiency, anemia, or bone lesions [CRAB]) or any other myeloma-defining event (MDE).[2] According to this recent update, the definition of SMM excludes asymptomatic patients with BMPCs of 60% or more, serum free-light chain (FLC) levels of 100 or greater, and those with two or more focal lesions of the skeleton as revealed by MRI. The new criteria were introduced because independent studies showed that patients with these features have an ultra-high risk of progression to MM (80% to 90% at 2 years), and that they should therefore be considered as patients with MM.

The incidence of SMM differs from one series to another, and the median age of the patients at diagnosis, as with other plasma cell disorders, ranges from 65 to 70 years.[3] Kristinsson et al, through the Swedish Myeloma Registry, recently reported that 14% of patients diagnosed with myeloma had SMM and, taking the world population as a reference, that the age-standardized incidence of SMM was 0.44 cases per 100,000 people.[4]

In this article, we focus on SMM, evaluate the prognostic factors that predict progression to symptomatic MM, and ex-

amine how patients may be managed, particularly with respect to the possibility of early treatment.

DIFFERENTIAL DIAGNOSIS WITH OTHER ENTITIES

SMM must be distinguished from other plasma cell disorders, such as monoclonal gammopathy of undetermined significance (MGUS) and symptomatic MM (Table 1). The MGUS entity is characterized by a level of serum M-protein of less than 3 g/dL plus less than 10% of plasma cell infiltration in the bone marrow, with no CRAB and no MDE. Symptomatic MM must always have CRAB symptomatology or MDE, in conjunction with a minimum of 10% clonal BMPC infiltration or biopsy-proven bony or extramedullary plasacytoma.[2]

End-organ damage often needs to be correctly evaluated to distinguish myeloma-related symptomatology from some signs or symptoms that could otherwise be attributed to comorbidities or concomitant diseases,[3] such as anemia due to iron, vitamin B12 or folic acid deficiency, or to the presence of autoimmune or chronic diseases, or myelodysplastic syndromes. In the case of moderate or severe renal impairment, patients with hypertension or diabetes should be carefully assessed. In patients who have isolated hypercalcemia without bone lesions, the presence of hyperparathyroidism should be considered, and diffuse osteoporosis should always be carefully evaluated, especially in women, to determine whether it is related to myeloma. If osteoporosis starts suddenly or is more extensive than expected for someone of the patient's

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TABLE 1. Differential Diagnosis of MGUS, SMM, and Symptomatic MM

Feature	MGUS	SMM	MM
Serum-M protein	< 3 g/dL and	≥ 3 g/dL and/or	
Clonal BMPC infiltration	< 10%	10-60%	≥ 10% or biopsy-proven plasmacytoma
Symptomatology	Absence of CRAB*	Absence of MDE** or amyloidosis	Presence of MDE**

Abbreviations: MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma; MM, multiple myeloma; BMPC, bone marrow plasma cell; CRAB, hypercalcemia, renal failure, anemia, and bone; MDE, myeloma-defining event. *CRAB includes (1) hypercalcemia: serum calcium > 0.25 mmol/L (> 1 mg/dL) higher than the upper limit of normal or > 2.75 mmol/L (> 11 mg/dL); (2) renal insufficiency: serum creatinine > 177 μmol/L (2 mg/dL) or creatinine clearance < 40 mL/minute; (3) anemia: hemoglobin value of > 2 g/dL below the lower normal limit, or a hemoglobin value < 10 g/dL; (4) bone lesions: one or more osteolytic lesion revealed by skeletal radiography, CT, or PET-CT. **MDE: Myeloma-defining events include CRAB symptoms (above) or any one or more of the following biomarkers of malignancy: clonal bone marrow plasma cell percentage ≥ 60%; involved/uninvolved serum free light-chain ratio ≥ 100; > 1 focal lesions revealed by MRI studies.

age, then myeloma-related symptomatology should be considered. Finally, if there is a single bone lesion present with no other symptoms, it is essential to rule out the presence of a benign bone cyst.

DIAGNOSTIC EVALUATION

Initial investigation of a patient with suspected SMM should include the tests shown in Sidebar 1, which are coincidental

KEY POINTS

- Smoldering multiple myeloma is not a homogeneous plasma cell disorder and includes patients at low, intermediate, and high risk of progression to symptomatic multiple myeloma.
- All newly diagnosed SMM patients should be stratified according to their risk.
- It is essential to identify asymptomatic patients at high risk of progression to symptomatic disease, in which the progression risk is 50% at 2 years following diagnosis, because they require close follow-up and, if possible, inclusion in clinical trials.
- Although the standard of care has been not to administer treatment until symptoms arise, early treatment with lenalidomide plus dexamethasone has helped change the treatment paradigm for patients with high-risk SMM.
- The updated International Myeloma Working Group criteria allow us to initiate therapy in patients who would previously have been considered asymptomatic on the basis of the absence of calcium, renal insufficiency, anemia, or bone lesions (CRAB) features, but who possess a specific biomarker predicting ultra-high risk of progression.
- In the future, novel therapeutic approaches will determine whether early treatment of patients with asymptomatic high-risk disease can definitively prevent the development of myeloma-related symptoms.

SIDEBAR 1. Evaluation of Patients Newly Diagnosed With SMM

- Medical history and physical examination
- Hemogram
- Biochemical studies, including of creatinine and calcium levels; beta 2-microglobulin, LDH, and albumin
- Protein studies
  - Total serum protein and serum electrophoresis (serum M-protein)
  - 24-hour urine sample protein electrophoresis (urine M-protein)
  - Serum and urine immunofixation
- Serum free light-chain measurement (FLC ratio)
- Bone marrow aspirate with or without biopsy: infiltration by clonal plasma cells, flow cytometry, and fluorescence in situ hybridization analysis
- Skeletal survey, CT, or PET-CT
- MRI of thoracic and lumbar spine and pelvis; ideally whole-body MRI

Abbreviations: SMM, smoldering multiple myeloma; LDH, lactate dehydrogenase; PET-CT, ^{18}F-fluorodeoxyglucose (FDG) PET/CT.

with those used for a correct diagnosis of symptomatic MM.[5] However, as result of the updated IMWG criteria for the diagnosis of MM, there are some specific assessments to be aware of in order to make a correct diagnosis of SMM.[2]

First, the IMWG recommends that bone disease be evaluated by x-ray, [18F]fluorodeoxyglucose (FDG) PET/CT or low-dose whole-body CT in all patients with suspected SMM, with the exact modality determined by availability and resources. The aim is to exclude the presence of osteolytic bone lesions, currently defined by the presence of at least one lesion (≥ 5 mm) revealed by x-ray, CT, or PET-CT. In addition, a whole-body MRI of the spine and pelvis is a necessary component of the initial evaluation. It provides detailed information about not only bone marrow involvement, but also the presence of focal lesions that predict more rapid progression to symptomatic myeloma. Hillengass et al reported in 2010 that the presence of more than one focal lesion in whole-body MRI was associated with a substantially shorter median time to progression (TTP) to active disease (13 months) compared with the period when no focal lesions were present.[6] Kastritis et al reported similar results after the analysis of a subgroup of patients who underwent spinal MRI and were followed for a minimum of 2.5 years. The median TTP to symptomatic disease was 14 months when more than one focal lesion was present.[7] Therefore, if more than one focal lesion in MRI is present in patients with SMM, the disease should no longer be considered as SMM but as MM, according to the current IMWG criteria.

Second, with respect to bone marrow infiltration, the Mayo Clinic group evaluated BMPC infiltration in a cohort of 651 patients and found that 21 (3.2%) had extreme infiltration (≥ 60%).[8] This group of patients had a median TTP to active disease of 7.7 months, with a 95% risk of progression at 2

years. This finding was subsequently validated in a study of 96 patients with SMM, in whom a median TTP of 15 months was reported for the group of patients with extreme infiltration.[9] In a third study, six of 121 patients (5%) with SMM were found to have 60% or greater BMPC, and all progressed to MM within 2 years.[10] Therefore, if 60% or greater of clonal plasma cell infiltration is present either in bone marrow aspirate or biopsy, the diagnosis of SMM should be replaced by MM. Additional assessments, for example, by flow cytometry or by identifying cytogenetic abnormalities in SMM patients, are not obligatory but can help estimate the risk of progression to active disease.

Third, with respect to the FLC assay, Larsen et al studied 586 patients with SMM to determine whether there was a threshold FLC ratio that predicted 85% of progression risk at 2 years. They found a serum involved/uninvolved FLC ratio of at least 100 in 15% of patients and a risk of progression to symptomatic disease of 72%.[11] Similar results were obtained in a study by Kastritis et al from the Greek Myeloma Group. In their study of 96 SMM patients, 7% had an involved/uninvolved FLC ratio of at least 100 and almost all progressed within 18 months.[9] In a third study, the risk of progression within 2 years was 64%. Therefore, physicians must consider the FLC assay at the moment SMM is first suspected and if the involved/uninvolved ratio is 100 or higher, the diagnosis of MM is correct under these circumstances.

Once SMM has been diagnosed, considering the specific assessments mentioned above, the serum and urine M-component, hemoglobin, calcium, and creatinine levels should be re-evaluated 2 to 3 months later to confirm the stability of these parameters. The subsequent follow-up involves the same evaluation, but the frequency should be adapted on the basis of risk factors for progression to symptomatic MM.

RISK FACTORS PREDICTING PROGRESSION TO ACTIVE MM

Most patients diagnosed with SMM will progress to symptomatic MM and will need to start treatment. However, SMM is not a uniform disorder and once the diagnosis has been confirmed, the doctor should evaluate the risk of progression to symptomatic disease to plan an appropriate, risk-based follow-up, and to optimize the management of patients with SMM. This approach is different from that taken when MGUS is diagnosed. MGUS is a homogeneous disease in which the risk of progression to symptomatic disease is substantially lower than that of SMM (1% per year) and uniform over time. Therefore, the recommended follow-up would be once per year.

In the first and largest systematic study of SMM, the Mayo Clinic group retrospectively evaluated the prognosis of patients with SMM in a large cohort of 276 patients for whom long-term follow-up data were available and whose disease was defined homogeneously according to the conventional IMWG criteria ($\geq$ 3 g/dL serum M-protein and/or $\geq$ 10% BMPCs with no CRAB symptoms). The annual risk of progression from SMM to symptomatic MM was 10% per year

for the first 5 years, 5% per year during the following 5 years, and only 1% per year after 10 years.[12]

Several studies have reported possible predictors of progression to symptomatic MM, and this information is useful for physicians and could also be used to help explain to patients their risk of progression to active MM (Sidebar 2).

SIZE OF SERUM M-PROTEIN AND THE EXTENT OF MARROW INVOLVEMENT

The aforementioned Mayo Clinic study[12] defined three SMM subgroups according to BMPC infiltration and the size of the serum M-protein. Group 1 was characterized by a minimum of 3 g/dL of M-protein and 10% or more of plasma cells in bone marrow, with a median TTP to symptomatic MM of 2 years. Group 2 featured 3 g/dL or less of M-protein and 10% or higher of BMPCs M-protein with a median TTP of 8 years. Group 3 had a minimum of 3 g/dL of M-protein but less than 10% BMPC infiltration, resulting in a median TTP of 19 years.

IMMUNOPHENOTYPING AND IMMUNOPARESIS

Multiparameter flow cytometry (MFC) used to identify the immunophenotypic profile of plasma cells in SMM has been evaluated by the Spanish Myeloma Group. The presence of an aberrant BMPC phenotype (minimum of 95% phenotypically abnormal plasma cells, determined by MFC and defined as the overexpression of CD56 and CD19, CD45-negative and/or decreased reactivity for CD38) was reported to be the most important predictor of early progression from SMM to active MM.[13] The presence of immunoparesis (i.e., a decrease in one or two of the uninvolved immunoglobulins to 25% below the lowest normal value) also emerged as an important independent prognostic characteristic. Based on these two parameters, our group proposed a scoring system for patients with SMM that prognostically stratified patients with SMM into three groups with a median TTP of 23 months when the two risk factors were present, 73 months when only one was present, and TTP not reached when neither was present.[14]

SERUM FREE-LIGHT CHAIN RATIO

The Mayo Clinic group also evaluated the previously described patient population to identify the risk of progression to symptomatic myeloma on the basis of a FLC assay. A kappa/lambda FLC ratio of 0.125 or less or 8 or more was associated with an increased of progression to symptomatic MM. This parameter was added to their previous score, which considered the size of serum M-protein and BMPC infiltration, to refine the Mayo risk stratification model. This yielded three groups, with a median TTP of 1.9 years for the high-risk group, whose members exhibited all three defined risk factors.[15]

SIDEBAR 2. Smoldering MM: Markers Predicting Progression to Symptomatic MM

Features for Identifying High-Risk SMM: 50% at 2 Years
· Tumor Burden
  - ≥ 10% clonal plasma cell bone marrow infiltration plus
  - ≥ 3 g/dL of serum M-protein and
  - Serum free light-chain ratio of 0.125 or less or 8 or more
  - Bence Jones proteinuria positive from 24-h urine sample
  - Peripheral blood circulating plasma cells > 5 × 106/L
· Immunophenotyping Characterization and Immunoparesis
  - ≥ 95% of aberrant plasma cells by flow within the plasma cell bone marrow compartment plus
  - Immunoparesis (> 25% decrease in one or both uninvolved immunoglobulins relative to the lowest normal value)
· Cytogenetic Abnormalities
  - Presence of t(4;14)
  - Presence of del17p
  - Gains of 1q24
  - Hyperdiploidy
  - Gene Expression Profiling risk score > -0.26
· Pattern of serum M-Component Evolution
  - Evolving type: if M-protein ≥ 3 g/dL, increase of at least 10% within the first 6 months. If M-protein < 3 g/dL, annual increase of M-protein for 3 years
  - Increase in the M-protein to ≥ 3 g/dL over the three months since the previous determination
· Imaging Assessments
  - MRI: Radiologic progressive disease (MRI-PD) was defined as newly detected focal lesions (FLs) or increase in diameter of existing FL and a novel or progressive diffuse infiltration.
  - Positive PET/CT with no underlying osteolytic lesion

Abbreviations: MM, multiple myeloma; SMM, smoldering multiple myeloma; PET-CT, ^{18}F-fluorodeoxyglucose (FDG) PET/CT.

PERIPHERAL BLOOD CIRCULATING PLASMA CELLS

The Mayo Clinic group also evaluated the role of peripheral blood circulating plasma cells in 171 SMM patients and in those (15%) who had high levels of circulating plasma cells ($> 5 \times 10^6$/L and/or > 5% plasma cells per 100 cytoplasmic immunoglobulin (Ig)-positive mononuclear cells), the progression risk at 2 years was significantly higher than for patients with low levels (71% vs. 24%; p = 0.001).[16]

PATTERN OF SERUM M-COMPONENT EVOLUTION

The pattern of evolution of the monoclonal component during the course of the disease enabled two types of SMM to be identified: the evolving and the nonevolving. The evolving type was defined based on the analysis of 207 SMM patients with the following criteria: if the concentration of M-protein was 3 g/dL or greater at baseline, the evolving type featured an increase in M-protein of at least 10% within the first 6 months following diagnosis; if the concentration of M-protein was less than 3g/dL at baseline, the evolving type featured a progressive increase in M-protein in each consecutive annual measurement over a 3-year period.[17] The evolving pattern was recognized in 25% of patients, and was associated with a probability of progression of 45% at 2 years, with a median TTP to active MM of 3 years compared with 19 years for those with the nonevolving type. The Southwestern

Oncology Grup (SWOG) also found that patients with an increase in the M component of at least 3 g/dL during the 3 months since their previous determination had an associated risk of progression of approximately 50% at 2 years.[18]

BENCE JONES PROTEINURIA

Although Bence Jones proteinuria in the 24-hour urine sample can be replaced by the FLC ratio at the time of diagnosis of MM and related disorders, it continues to be a mandatory assessment during follow-up.[19] In one study, 147 patients with SMM were examined for the presence of Bence Jones proteinuria at diagnosis and its effect on progression to symptomatic disease was assessed. The study showed that in patients with SMM in whom the M-protein was defined by a complete Ig, but who were also positive for Bence Jones proteinuria regardless of the amount, the risk of progression to active disease was significantly higher than in patients who were negative for Bence Jones proteinuria (22 vs. 83 months; p < 0.001). In addition, when Bence Jones proteinuria in the 24-hour urine sample exceeded 500 mg, the risk was even higher, with a median TTP of 7 months.[20]

NOVEL IMAGING ASSESSMENTS

The novel imaging assessments have contributed to the updated criteria for the definition of MM and SMM, as has been

previously mentioned. However, the new imaging assessments can also help predict progression risk in patients with SMM. The first studies with spinal MRI were conducted in patients with asymptomatic MM and the presence of a focal pattern was associated with a shorter TTP than those patients with a diffuse or variegated pattern (median, 6 vs. 16 vs. 22 months, respectively). Hillengass et al recently evaluated the role of MRI during the follow-up of patients with SMM. Radiologic progressive disease (MRI-PD), defined as the detection of new focal lesions or the increase in diameter of existing focal lesions, and a novel or progressive diffuse infiltration was identified as a feature for classifying patients with SMM at high risk of progression to symptomatic disease.[21] The role of PET/CT has also been evaluated in SMM. The Italian group recently reported that in a series of 73 patients with SMM, approximately 10% had a positive result with PET/CT with no underlying osteolytic lesion and were predicted to be at high risk of progression to symptomatic disease (48% at 2 years compared with 32% for PET/CT-negative patients; p = 0.007).[22] The Mayo Clinic group also identified a subgroup within a series of 132 patients with SMM who had a positive result with PET/CT in which the rate of progression to MM within 2 years was 56% compared with 28% among patients who had a negative PET/CT result (p = 0.001). The rate of progression was even higher among patients in whom PET/CT was performed within 3 months of their diagnosis of SMM (74% vs. 27% in PET/CT-negative patients).[23]

CYTOGENETIC ABNORMALITIES

Neben et al have identified t(4;14), gain of 1q21, or hyperdiploidy as independent prognostic factors of shorter TTP. The median TTP for patients with del(17p13) was 2.7 years compared with 4.9 years for patients without the deletion (p = 0.019), 2.9 years for patients with t(4;14) compared with 5.2 years for patients without the deletion (p = 0.021), and 3.7 years for patients with +1q21 compared with 5.3 years for those without the deletion (p = 0.013). In addition, hyperdiploidy was associated with a significantly shorter median TTP of 3.9 years compared with 5.7 years for patients without hyperdiploidy (p = 0.036).[24] The Mayo Clinic group also analyzed the cytogenetic abnormalities in a series of 351 patients with SMM and identified a high-risk subgroup of patients with t(4;14) and/or del(17p) with a substantially shorter median TTP (24 months) than the intermediate-, standard- and low-risk patient subgroups.[25] Finally, the SWOG evaluated the Gene Expression Profiling 40 (GEP40) model in a group of 105 patients with SMM, and estimated 7.05 to be the optimal cut point for risk of progression to active disease. The 3-year TTP probability was 83% compared with only 11% for patients with scores below this threshold.[26]

In summary, the diagnosis of SMM is associated with a variable risk of progression to active disease, and the presence of the aforementioned prognostic factors can discriminate subgroups of patients with respect to their degree of risk (Sidebar 2).

MANAGEMENT OF SMM

The standard of care for the management of SMM was observation until MM develops. However, because of the heterogeneity of the disease, several groups evaluated the role of early intervention in patients with SMM using conventional and novel agents.

Three small studies compared early therapy consisting of melphalan and prednisone (MP) with observation alone. In the Hjorth study, the response rate to therapy in patients treated at diagnosis was similar to that of patients who received deferred therapy at the time of progression (52% vs. 55%).[27] In the other two trials, there were no differences in OS between early treatment and observation (54 vs. 58 months in the former, and 64 vs. 71 months in the latter).[28,29] Two small phase II trials, one by the Mayo Clinic and the other by The University of Texas MD Anderson Cancer Center, evaluated the role of thalidomide as a single agent in patients with SMM.[30,31] The rates of partial response (PR) or better were 34% and 36%, respectively, and most patients who discontinued treatment did so because of peripheral neuropathy. Barlogie et al conducted another nonrandomized phase II trial with thalidomide plus pamidronate in 76 patients with SMM, obtaining a PR rate of at least 42%, with a 6-year median TTP to symptomatic disease. The development of peripheral neuropathy was the main problem in patients who received long-term thalidomide treatment.[32] Novel agents have also been evaluated in SMM. Anakinra is an antagonist of the receptor of interleukin (IL)-1 and produced stabilization of the disease (in 8 patients), minor responses (3 patients), and partial responses (5 patients) in a group of 47 patients with SMM, with a median TTP of 37 months.[33] A phase II study of an anti-KIR monoclonal antibody in 21 patients found no clinical response.[34] Immunotherapy using a vaccine consisting of peptides from unique regions of three MM-associated antigens is currently being evaluated in patients with SMM and is producing promising efficacy results.[35] It is difficult to draw firm conclusions from the results of these trials, only one of which was randomized, although we can be confident that approximately one-third of patients with SMM responded to thalidomide. Only one randomized trial has compared the outcome of thalidomide plus zolendronic acid and that of zolendronic acid alone in patients with SMM. The rate of PR was a minimum of 37% in the thalidomide arm compared with 0% in the zoledronic acid–only arm, but there were no differences in the TTP to symptomatic MM (4.3 vs. 3.3 years) or in the 5-year OS (74% vs. 73%).[36] The role of bisphosphonates has also been analyzed in three trials, considering pamidronate as a single agent in one of them,[37] pamidronate versus abstention in another,[38] and zolendronic acid versus observation in the third.[39] All three studies confirmed that bisphosphonates have no antitumoral effect but reported an increase in bone density and a decrease in bone resorption, both of which were related to the bone markers. It is important to note that in the two randomized trials comparing bisphosphonates with abstention, a substantial reduction in the incidence of skeletal-related events in the bisphosphonate arms

was reported at the moment of progression to active MM (39% vs. 73% and 55% vs. 78%).

None of these trials provided evidence favoring the early treatment of patients with SMM. However, they were conducted without considering the differences in the risk of progression to active disease, and although the high-risk subgroup of patients may have benefited, this could have been counterbalanced by the absence of benefit in low-risk patients. The Spanish Myeloma Group (GEM/Pethema) conducted a phase III randomized trial in 119 patients with SMM at high risk of progression to active disease (according to the Mayo and/or Spanish criteria) that compared early treatment with lenalidomide plus dexamethasone as induction followed by lenalidomide alone as maintenance versus observation. The primary endpoint was TTP to symptomatic MM, and after a median follow-up of 40 months, the median TTP was significantly longer in patients in the early treatment group than in the observation arm (not reached vs. 21 months; hazard ratio [HR] 5.59; p < 0.001). Secondary endpoints included response, OS, and safety. The PR or better after induction was 82%, including 14% of cases of stringent complete response (sCR) plus CR, and after maintenance the sCR/CR rate increased to 26%. The safety profile was acceptable and most of the adverse events reported were grade 1 or 2. The OS analysis showed that the 3-year survival rate was also higher for the group of patients who received early treatment with lenalidomide-based therapy (94% vs. 80%; HR, 3.24; p = 0.03).[40] A recent update of this trial confirmed the efficacy of early treatment in terms of TTP (HR 6.21; 95% CI, 3.1 to 12.7; p < 0.0001) and the benefit to OS was even more evident with longer follow-up (HR 4.35; 95% CI, 1.5 to 13.0; p = 0.008).[41] This study showed for the first time the potential for changing the treatment paradigm for high-risk patients with SMM based on the efficacy of early treatment in terms of TTP to active disease and of OS. Moreover, several trials that are currently underway are focusing on high-risk patients with SMM using novel agents such as lenalidomide alone, siltuximab (anti-IL6 monoclonal antibody), elotuzumab (anti-SLAMF7 monoclonal antibody), or lenalidomide-dexamethasone plus elotuzumab. Promising efficacy results have been reported for the combination of lenalidomide plus dexamethasone with the novel proteasome inhibitor carfilzomib in a series of 12 high-risk patients with SMM. All patients achieved CR and most were in immunophenotypic CR.[42] The next step will be to develop a more intensive approach to therapy for high-risk patients with SMM, similar to the treatment planned for young patients with symptomatic MM, for whom "cure" should be the objective.

MANAGING SMM IN CLINICAL PRACTICE: WHEN TO OBSERVE AND WHEN TO TREAT

Given the extensive background to this disease described above, the first step in clinical practice is to identify the risk of progression to active disease for each patient newly diagnosed with SMM. The key question is which risk model is better for evaluating the risk of progression to symptomatic disease for

each individual patient with SMM. The Mayo Clinic and Spanish models enable initial risk stratification of SMM and both were validated in a prospective trial. However, new risk models are emerging that incorporate new clinical and biologic features (Table 2).[10,12,14,17,18,24,43,44] The components of these models are not identical, and each patient's risk should probably be defined on the basis of all the available data rather than through the use of a restricted model (Sidebar 2).

CLASSIFYING PATIENTS WITH SMOLDERING MULTIPLE MYELOMA

Patients with SMM should be classified as follows:

(1) The first group includes patients at low risk of progression who are characterized by the absence of the aforementioned high-risk factors (using the validated Mayo and Spanish risk models), with a probability of progression at 5 years of only 8%. The patients in this group behave similarly to patients with MGUS and should be followed annually.

(2) The second group includes patients at intermediate risk of progression, who display only some of the aforementioned high-risk factors. These are probably the patients with true SMM. The risk of progression at 5 years is 42%, and patients should undergo follow-up every 6 months.

(3) The third group includes high-risk patients classified on the basis of one of the risk models mentioned above. Half of the patients will progress during the 2 years following diagnosis. These patients require close follow-up every 2 to 3 months. The key question is whether this high-risk group should be treated. Although the Spanish trial showed substantial benefit from the early treatment in high-risk patients with SMM, there are some limitations that prevent the results being generally applicable at present; these may be resolved when the results of the ongoing clinical trials become available. The best approach for these patients should be to refer them to centers specialized in MM therapy and to include them in clinical trials to better understand their biology and to confirm the survival benefit of early treatment in this cohort.[45]

As mentioned at the beginning of the review, the updated IMWG criteria have enabled us to define patients with MM as those who would have been considered in the past as having SMM due to the presence of specific biomarkers such as 60% or greater BMPCs, or a serum FLC level of 100 or higher, or at least two focal lesions of the skeleton as revealed by MRI. These patients can begin treatment on diagnosis without the presence of CRAB features.

FUTURE DIRECTIONS

The treatment philosophy for patients with MM has mainly focused on symptomatic patients. This approach is clearly different from those adopted to treat other malignancies, such as cancers of the breast, colon, or prostate, for which

TABLE 2. Risk Models for the Stratification of SMM

Risk Model	Risk of Progression to MM	
Mayo Clinic		**Median TTP (years)**
≥ 10% clonal PCBM infiltration	1 risk factor	10
≥ 3 g/dL of serum M-protein	2 risk factors	5
Serum FLC ratio between < 0.125 or > 8	3 risk factors	1.9
Spanish Myeloma		**Median TTP (years)**
≥ 95% of aberrant PCs by MFC	No risk factor	NR
Immunoparesis	1 risk factor	6
	2 risk factors	1.9
Heidelberg		**3-year TTP**
Tumor mass using the Mayo Model	T-mass low + CA low risk	15%
t(4;14), del17p, or +1q	T-mass low + CA high risk	42%
	T-mass high + CA low risk	64%
	T-mass high + CA high risk	55%
SWOG		**2-year TTP**
Serum M-protein ≥ 2 g/dL	No risk factor	30%
Involved FLC > 25 mg/dL	1 risk factor	29%
GEP risk score > −0.26	≥ 2 risk factors	71%
Penn		**2-year TTP**
≥ 40% clonal PCBM infiltration	No risk factor	16%
sFLC ratio ≥ 50	1 risk factor	44%
Albumin ≤ 3.5 mg/dL	≥ 2 risk factors	81%
Japanese		**2-year TTP**
Beta 2-microglobulin ≥ 2.5 mg/L	2 risk factors	67.5%
M-protein increment rate > 1 mg/dL/d		
Czech & Heidelberg		**2-year TTP**
Immunoparesis	No risk factor	5.3%
Serum M-protein ≥ 2.3 g/dL	1 risk factor	7.5%
Involved/uninvolved sFLC > 30	2 risk factors	44.8%
	3 risk factors	81.3%
Barcelona		**2-year TTP**
Evolving pattern = 2 points	0 points	2.4%
Serum M-protein ≥ 3 g/dL = 1 point	1 point	31%
Immunoparesis = 1 point	2 points	52%
	3 points	80%

Abbreviations: SMM, smoldering multiple myeloma; MM, multiple myeloma; TTP, time to progression.

early intervention is not only appropriate, but also essential for success and cure. This difference in philosophy arose for several reasons: 1) in the past, only a few drugs, most of which were alkylating agents, were available to treat MM; 2) the trials conducted in asymptomatic patients with MM failed to produce a benefit; and 3) the risk of progression to active disease in patients with SMM is relatively low (10% per year).

However, important advances are being made in the understanding and management of SMM. From the biologic point of view, different subgroups of patients with SMM have been identified and patients with MM should receive antimyeloma therapy be started before myeloma-related symptoms develop. Additional studies will help us better understand the biology of the disease and identify the key drivers of the transition from monoclonal gammopathy to smoldering and symptomatic disease. These drivers will be considered as targets for new therapies.

We will soon have the results from several current trials conducted in high-risk patients with SMM, which will enable us to offer early treatment for a selected group of asymptomatic patients with myeloma with the confidence that some of them will be "cured." The cure-versus-control debate is pertinent to asymptomatic patients with myeloma. Some physicians argue in favor of controlling the disease through continuous oral therapy mainly based on immunomodulatory agents, whereas others support the intensive therapy approach, including high-dose therapy and transplant, with the objective of curing the disease.

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Relationships are considered self-held and compensated unless otherwise noted. Relationships marked "L" indicate leadership positions. Relationships marked "I" are those held by an immediate family member; those marked "B" are held by the author and an immediate family member. Institutional relationships are marked "Inst." Relationships marked "U" are uncompensated.

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Multiple Myeloma: Is It Time for Biomarker-Driven Therapy?

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OVERVIEW

Remarkable strides have been made in understanding the molecular mechanisms by which multiple myeloma develops, leading to more sophisticated classification that incorporates not only the traditional diagnostic criteria, but also immunophenotype, genetic, and molecular features. However, even with this added information, considerable heterogeneity in clinical outcomes exists within the identified subtypes. The present paradigm for myeloma treatment is built on the basic step of defining transplant eligibility versus noneligibility, as determined by age, performance status, and cumulative burden of comorbidities. An incredibly complex heterogeneous disease is, therefore, treated in a generalized way with the result that large interpatient variability exists in the outcome. As antimyeloma therapeutics continue to expand it is becoming even more crucial to personalize treatment approaches that provide the most value to a specific patient. Development of biomarkers, either individually or as larger sets or patterns and ranging from analysis of blood or bone marrow to biomedical imaging, is a major focus in the field. Biomarkers such as involved serum free light chain ratio and MRI focal lesions have been implemented in the new definition of multiple myeloma and guide clinicians to initiate treatment in otherwise asymptomatic individuals. Currently, however, there is not enough evidence to support intensifying the treatment for high-risk disease or reducing the treatment for low-risk disease. Minimal residual disease-negative status is an important biomarker that holds promise for monitoring the effectiveness of response-adapted strategies. This article sheds light on the forward landscape and rear-mirror view of biomarkers in myeloma.

The outcome for patients with multiple myeloma (MM) has considerably improved over the last decade with the incorporation of active agents including immunomodulatory drugs (IMiDs) and proteasome inhibitors, such that the median survival of newly diagnosed patients is now between 5 and 9 years.[1,2] Increasingly effective salvage therapies have resulted in durable remission as well as long-term survival for selected patient subgroups. Nonetheless, despite these advances the current therapy for MM remains noncurative, and a subset of cases show a rapidly relapsing and refractory disease course. Myeloma therapy is currently based on studies that largely predate the molecular classification, and most patients are treated by the conventional one-size-fits-all therapeutic approach. Over recent years, great progress has been made in our understanding of the key genetic abnormalities, central signaling pathways, the role of the bone marrow microenvironment, and monitoring of minimal residual disease (MRD). It is undoubtedly clear that there is extensive heterogeneity, not only between patients but also within patients, resulting from complex genetics and clonal evolution during the course of disease. The MM genome is extremely complex, with approximately 35 nonsynonymous mutations identified per case.[3] Underlying this vast landscape of genetic alterations are multiple deregulated core signaling pathways and

mutations of diagnostic and therapeutic significance that open several possible avenues for the optimization of risk-adapted strategies and biomarker-focused clinical trials in MM.[3,4]

A biomarker is typically defined as any characteristic (e.g., gene, protein, clinicopathologic variable, imaging feature) that can be objectively and reproducibly measured to serve as an indicator of disease biology or response to a therapeutic intervention.[5] For clinical purposes, disease-related biomarkers assist in diagnosis, prognosis, and response monitoring. Drug-related biomarkers, on the other hand, indicate whether a drug will be effective in a specific patient and how the patient's body will process it. Within the context of a clinical trial, an integral biomarker is defined as a marker that must be measured in real time for the trial to proceed, for example when the test is used to establish eligibility, treatment assignment, or stratification, or to detect early response to decide further treatment.[6] In contrast, integrated biomarkers are measured during the clinical trial; however, their results do not determine the treatment or course of the ongoing trial, but instead inform future studies.[6] Biomarker research in myeloma continues to advance in many spheres. The first pertains to biomarkers that aid in risk stratification of patients and provide guidance in the selection or titration

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of therapeutic agents. Second, it is becoming increasingly apparent that certain biomarkers offer the promise of distinguishing aggressive from indolent disease evolution, such that individuals most at risk of progressing from precursor states to MM can be targeted at the earliest and most treatable stage. The third area of thrust is biomarkers of benefit, which indicate the effect of therapeutic intervention and predict sensitivity or resistance, and thus correlate with outcomes. Additionally, the technologies for standardization and interpretation of MRD continue to evolve. Clinical trials based on integral and integrated biomarkers remain a key area of research, and correlative science within the context of these trials will be vital in determining the significance of defined biomarkers. We provide an overview of the current knowledge in each area in which biomarkers are being explored in MM. In addition, we discuss the potential and limitations of designing biomarker-driven clinical trials.

MONOCLONAL PROTEIN BIOMARKERS

Myeloma-related plasma cell disorders are typically characterized by monoclonal protein biomarkers, which can be in the form of intact immunoglobulin, immunoglobulin fragments, or free immunoglobulin light chains (FLC), in either the serum or urine. These biomarkers play an important role in diagnosis and response monitoring. One of the earliest identified biomarkers is Bence Jones protein, which was described in 1848.[7] A cutoff of serum monoclonal protein of 3 g/dL or greater and/or bone marrow plasmacytosis of at least 10% is used to distinguish smoldering multiple myeloma (SMM) from monoclonal gammopathy of undetermined significance (MGUS).[8] During the past decade the measurement of serum kappa and lambda FLC has also become part of routine clinical testing. An abnormal FLC ratio indicates

KEY POINTS

- Intra- and interpatient heterogeneity in multiple myeloma underscores the need for personalized treatment approaches.
- New International Myeloma Working Group 2014 biomarker-based definitions identify a subset of patients that require therapy in the absence of clinical manifestations of serious end-organ damage.
- At present, there is no strong evidence for escalating or de-escalating therapy based on favorable, standard, and high-risk categories.
- The new generation of biomarkers—including epigenetics, novel imaging, clone burden, GEP signature, and next-generation sequencing—coupled with established prognostic biomarkers holds promise for improved stratification of patients with myeloma into specific therapies and clinical trials.
- Improvement in patient outcomes can be achieved through adaptive clinical trials involving risk models based on multiple biomarkers.

the presence of clonality in approximately one-third of patients with MGUS and in at least 90% of patients with MM.[9] The assay is particularly indicated for the diagnosis and follow-up of patients with nonsecretory and oligosecretory myeloma, light chain myeloma, and amyloidosis.[10] Revised International Myeloma Working Group (IMWG) 2014 criteria define myeloma biomarkers that indicate a requirement for therapy in asymptomatic individuals, including bone marrow plasmacytosis of 60% or greater and involved FLC ratio greater than 100 (Table 1).[11] In an era of broadened treatment options, there are substantial data showing the association of depth of response and outcome. Following treatment, complete response (CR) criteria include negative immunofixation of serum and urine and the presence of less than 5% plasma cells. Normalization of the FLC ratio plus the absence of clonal plasma cells by immunochemistry or immunofluorescence is considered a deeper level of response that is termed stringent CR (sCR).[12] Achievement of CR is considered one of the strongest prognostic biomarkers in MM, both in the transplant and nontransplant settings, although the sCR criteria have failed to unequivocally demonstrate superior prognostic value compared with CR.[13,14] More sensitive ways of measuring CR are required when results from serum protein electrophoresis are difficult to interpret, including problems resulting from polyclonal immunoglobulins, comigration of monoclonal bands, and poor sensitivity at low levels of monoclonal protein (<10 g/L). These drawbacks could be overcome by the new U.S. Food and Drug Administration (FDA)-approved heavy/light chain (HLC) assay (Hevylite). The unique ability of this assay to measure suppression of the uninvolved HLC pair (e.g., IgG-lambda, IgA-kappa, and IgA-lambda for a patient with IgG-kappa disease) adds sensitivity for monitoring disease response and detecting residual disease. The HLC ratio reflects the balance between monoclonal and polyclonal immunoglobulins of involved and uninvolved isotypes taking into account the polyclonal plasma cell suppression or expansion that occurs with the treatment. A few studies have shown that this assay affords additional prognostic information in MGUS and MM.[15,16] If confirmed by other studies and long-term follow-up, HLC could be a noninvasive marker of response.

CYTOGENETICS AND FISH BIOMARKERS

Many studies have reported on the prognostic value of cytogenetics and fluorescence in situ hybridization (FISH) biomarkers; however, some have yielded conflicting results.[17-21] Reasons for these discrepancies include retrospective analyses, small sample size, variable techniques, lack of a standard definition of high risk, and failure to control for other biologic or treatment processes that may confound the outcome. In general, t(14;16), t(14;20), and del(17p) are associated with a poor prognosis, whereas t(11;14), t(6;14), and hyperdiploid myeloma are considered to impart standard risk, provided there are no additional adverse features such as +1q21 and del(17p) (Table 1).[22] Trisomies are typically associated with a

TABLE 1. The Changing Biomarker Landscape

Biomarkers	Old	Updated	Future
Smoldering Multiple Myeloma			
Diagnostic	≥ 10% clonal marrow plasma cells*	10% to 60% clonal marrow plasma cells	High circulating clonal plasma cells by flow cytometry
	≥ 3 g/dL serum M-protein	Urinary M-protein ≥ 500 mg per 24 h	10% increase in M-protein within 6 months
Prognostic	Serum free light-chain ratio 0.125 to 8; Immunoparesis; ≥ 95% marrow plasma cells of aberrant phenotype** by flow cytometry		High bone marrow plasma cell proliferative rate; GEP 70 Risk score ≥ 0.26; Cytogenetic subtypes: t(4;14), 1q amp, or del 17p
Multiple Myeloma			
Diagnostic	Clonal bone marrow plasma cells ≥ 10% or biopsy-proven bony or extramedullary	Clonal marrow plasma cell ≥ 60%	
	Plasmacytoma PLUS	Involved:uninvolved serum free light chain ratio‡ ≥ 100	
	CRAB myeloma defining events	> 1 focal lesion on MRI§	
		CRAB events including bone lesions on CT or PET/CT	
Low/Standard Risk†	Trisomies	ISS I/II and NO t(4;14) or del 17p13	New GEP-based prognostic signatures
	Hyperdiploidy	Age < 55	
	ISS I		
	t(11;14)		
	t(6;14)		
Standard/Intermediate Risk	ISS II	t(4;14)	
		1q gain	
		Deletion 13 or hypodiploidy by conventional karyotyping	
		Complex karyotype	
		Plasma cell labeling index > 3%	
High Risk	ISS III	ISS II/III plus t(4;14) or del 17p13	
	Monosomy 13	t(14;16)	
	Hypodiploidy	Plasma cell leukemia	
	t(4;14)	LDH ≥ 2 ULN	
		GEP 70 High Risk Signature	
Treatment/Response	CR	sCR	MRD-negative
		Immunophenotypic CR	HLC ratio
			Immune signature
			Proteasome signature
			IMiD signature
			Clone burden/Clone status
Imaging Prognostic	Skeletal survey lytic lesions	MRI focal lesions > 7	Novel PET probes
		FDG/PET focal lesions > 3	DCE-MRI diffusion/perfusion

Abbreviations: LDH, lactate dehydrogenase; ULN, upper limit of normal; sCR, stringent CR; GEP, gene expression profiling; MRD, minimal residual disease; IMiD, immunomodulatory drugs; DCE-MRI, dynamic contrast enhanced-magnetic resonance imaging.

*Clonality should be established by the demonstration of κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in cases of disparity between the aspirate and core biopsy, the highest value should be used. M-protein: monoclonal protein.

**Aberrant immunophenotype of plasma cells on flow cytometry: absence of CD19 and/or CD45 expression, overexpression of CD56, or weak expression of CD38. CRAB: hypercalcemia, renal insufficiency, anemia, and bone lesions.

†Mayo Clinic risk classification includes standard risk, intermediate risk, and high-risk categories; International Myeloma Working Group consensus risk classification includes low risk, standard risk, and high-risk categories. ISS: International Staging System: stage I: serum beta-2 microglobulin < 3.5 mg/L, albumin ≥ 3.5 g/dL; stage II: beta-2 microglobulin between 3.5 and 5.5, or albumin < 3.5 g/dL; stage III: beta-2 microglobulin ≥ 5 mg/L. CR: complete response.

‡These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥ 100 mg/L.

§Each focal lesion must be at least 5 mm in size. PET-CT: ^{18}F-fluorodeoxyglucose PET with CT.

better prognosis, except when associated with gains of 1q and monosomy of chromosome 13. Gain of 1q is seen in approximately 40% of newly diagnosed cases, and has been linked to adverse prognosis in patients treated intensively with or without IMiDs.[23,24] Although monosomic 13/13q deletion (present in approximately 50% of cases) has been typically associated with an unfavorable prognosis when detected by conventional cytogenetics,[25] the prognostic implication of this abnormality is difficult to assess because of its close association with other high-risk genetic features, such as t(4;14), in 80% of cases.[19] Approximately 32% of patients presenting with MM have a deletion of 1p affecting *FAF1* and *CDKN2C*, which has been associated with short survival.[26] Some of these biomarkers have treatment-specific prognostic implications; for example, an approach that combines bortezomib-based therapy for 2 to 3 years in conjunction with tandem autologous stem cell transplantation (ASCT) has been shown to abrogate or attenuate the prognostic influence of t(4;14).[27,28] No single genetic abnormality by itself defines high-risk MM and it is important to determine the presence or absence of a panel of cytogenetic abnormalities to properly identify patients with adverse prognosis.

INTERNATIONAL STAGING SYSTEM

The International Staging System (ISS) was developed as a multicenter effort before IMiDs and proteasome inhibitors became available and has been the primary clinical tool used to predict outcome.[29] This system stratifies patients into three groups based on serum albumin and β2-microglobulin. Although the ISS remains prognostic within clinical trials, this system has limited utility for assessing risk on an individual patient basis and does not take into account genetic abnormalities and the role of intrinsic myeloma cell variability to allow for tailored therapy approaches. Importantly, the ISS and FISH/cytogenetic abnormalities can be combined in a prognostic model (Table 1).[11] There are good data supporting the application of a combined approach for risk prognostication in the design of biomarker-focused clinical trials.[30]

GENE EXPRESSION PROFILING BIOMARKERS

Global gene expression profiling (GEP) is an alternative technology that integrates the influence of multiple genetic abnormalities on important cellular pathways associated with proliferation, differentiation, apoptosis, and other biologic features in a single signature. The University of Arkansas for Medical Sciences (UAMS) group was the first to define a 70-gene classifier (GEP70) characterizing 7 distinct gene expression clusters that identified patients with high risk for short progression-free survival (PFS) and overall survival (OS).[31] The prognostic significance of the UAMS GEP70 assay has been validated in several studies performed independently by U.S. and international groups. In another study, GEPs obtained from patients with newly diagnosed MM included in the HOVON65/GMMG-HD4 trial were used to generate a

prognostic signature of 92 genes (EMC-92-gene signature) capable of distinguishing between patients with high risk and low risk that was subsequently confirmed in independent validation sets of newly diagnosed and patients who relapsed.[32] Other signatures linked to short survival have been defined, including a 17-gene signature identified by UAMS, a 15-gene signature in the IFM trials, and a 6-gene signature in the MRC Myeloma IX trial.[33,34] Interestingly, the 17-, 15-, and 6-gene signatures do not share any common genes, reflecting variation in treatment strategies or patient selection between studies, or perhaps different aspects of myeloma biology. Although GEP provides valuable information regarding disease biology in the context of clinical trials, more work is required to define a standardized user-friendly GEP signature that can be more widely applied as a prognostic tool in clinics. To this end, the International Myeloma Working Group (IMWG) is conducting a study to unify the GEP signatures using prognostic modeling.

FLOW CYTOMETRIC BIOMARKERS AND MRD MONITORING

Flow cytometric methods have become an integral part of diagnosis and monitoring in many hematologic malignancies, such as acute and chronic leukemias; however, consensus regarding their routine use in plasma cell disorders is still evolving. Multiparameter flow cytometry (MFC) allows quantification and characterization of clonal plasma cells through their aberrant phenotypes rather than by light chain restriction. The immunophenotypic features of plasma cells vary depending on the diagnosis, stage of disease, and the type of therapies employed. Multiple studies have demonstrated the prognostic value of specific patterns of antigen expression by neoplastic plasma cells; for example CD19+, CD28+, CD81+, or CD117− expression has been associated with inferior outcome.[35] Patient-specific immunophenotypic profiles with the sensitivity to detect one or more tumor cells in 10,000 normal cells make MFC an attractive strategy for MRD monitoring. From a clinical perspective, achieving an immunophenotypic CR predicts extended survival in younger patients undergoing intensive therapy and older patients treated with novel agents. The pitfalls of flow cytometric MRD assessment include its lack of standardization and the need for experienced personnel.[36,37] A recent survey across 30 major medical institutions in the United States found that immunophenotypic features defining abnormal plasma cells varied substantially among institutions, as did the sensitivity of the MFC assays for MRD, which exhibited a 100-fold difference ranging from 0.0005% to 0.02%.[38] The NCI, FDA, MMRF, and EuroFlow Consortium have initiated concerted efforts to overcome these drawbacks. In addition to MFC, polymerase chain reaction techniques are well standardized and highly sensitive (10^{-5} to 10^{-6}), with several studies showing that, among patients achieving a CR, MRD-negative status is associated with substantial improvements in PFS and OS.[39,40] However, designing allele-specific oligonucleotides for each individual is

laborious and time consuming, relatively expensive, and requires high-quality DNA, not only for post-treatment samples but also at baseline. Moreover, the genetic mutations are not stable longitudinally. Systematic assessment of MRD by next-generation sequencing (NGS) offers a novel platform with increased sensitivity, in particular for serial monitoring of mutational shifts between diagnosis and relapse.[41] Progression is characterized by dynamic clonal equilibrium resulting from multiclonal presentation, clonal dominance, and post-treatment clonal selection. With respect to the potential need for frequent MRD sampling, the question of whether NGS of peripheral blood plasma cells could replace bone marrow testing is being studied. It should be noted that MRD negativity does not equate with complete tumor eradication, particularly in a disease that is typically characterized by patchy marrow infiltration and extramedullary involvement. In parallel with standardizing assays and validating prognostic MRD thresholds, there is an increasing interest in MRD monitoring as a tool for risk-adapted clinical trials.[42]

IMAGING BIOMARKERS

Paralleling the improvements in laboratory techniques, great advances have been made in imaging biomarkers. For a disease like MM that is characterized by bone involvement in at least 80% of patients, imaging plays a critical role in diagnosis. The use of imaging biomarkers is as old as skeletal surveying itself; moreover, as the field of medical imaging has expanded to include MRI and PET, the number of available biomarkers has also increased. The principal imaging biomarkers are currently topographic markers such as lytic bone lesions and/or abnormal plasma cell proliferations in bone marrow or soft tissues. The major advantages of MRI and PET/CT compared with skeletal survey are discrimination between normal and invaded bone marrow, visualization of extramedullary disease (EMD) and cord involvement, and better sensitivity for lytic bone lesions. MRI and PET/CT biomarkers of focal marrow abnormalities (with or without osteolysis) provide a method to assess disease burden and prognosis and monitor response to therapy. The number of focal lesions at baseline on MRI or ^{18}F-FDG PET/CT adversely affected both OS and event-free survival (EFS), as did the presence of EMD and failure of FDG suppression. Specifically, more than three baseline PET focal lesions and more than seven baseline MRI focal lesions (present in 32% and 36% of newly diagnosed patients with MM, respectively) were each associated with shorter EFS and OS.[43-45] Moreover, complete suppression of FDG before the first ASCT conferred a favorable outcome.[44] Additionally, the absence of PET suppression by day 7 of the first induction cycle in patients with MM who were treated in the Total Therapy 3 trials was associated with inferior OS and PFS.[46] These observations have important implications and require further validation in the era of novel therapy induction regimens. PET/CT provides a complementary tool to biopsy for assessing heterogeneity and the effect of treatment within and across multiple disease sites. Emerging biomarkers, such as novel PET probes and dynamic contrast-enhanced (DCE) MRI parameters, including diffusion/perfusion, angiogenesis, and mismatches in tumor metabolism, provide a unique opportunity to evaluate response and resistance to antimyeloma therapy. Data demonstrating the efficacy of ^{11}C-thymidine PET and ^{18}F-fluorothymidine for response evaluation are promising.[47] Although the newer imaging biomarkers have not yet been fully validated, recent advances in functional and molecular imaging provide a wealth of opportunities and accumulating data suggest that these biomarkers will become increasingly important in the future.

BONE TURNOVER BIOMARKERS

Biomarkers of bone turnover (resorption and formation) are attractive noninvasive tools for detecting early bone involvement and for evaluating the risk of skeletal morbidity and response to antiresorptive treatment.[48] These markers can be divided into two categories: collagen fragments released from the bone matrix during degradation, and enzymes released from either osteoblasts or osteoclasts. Biomarkers reflecting osteoclast-mediated degradation of collagen, including N-terminal cross-linking telopeptide of type-1 collagen (NTX), C-terminal cross-linking telopeptide of type-1 collagen (CTX), C-terminal cross-linking telopeptide of type-1 collagen generated by metalloproteinase (ICTP), and deoxypyridinoline, provide information on the remodeling process and reflect whole-body bone turnover as opposed to local changes in skeletal homeostasis.[49] Urinary NTX, serum CTX, and serum ICTP levels are elevated in patients with MM and correlate with advanced osteolytic disease.[50-52] Furthermore, urinary NTX and serum ICTP correlate with risk for skeletal complications, PFS, and OS.[51,53,54] Procollagen type-1 N-propeptide and procollagen type-1 C-propeptide signify new bone formation.[55] Receptor activator of nuclear factor-kappa B ligand (RANKL) and osteoprotegerin are also important markers of bone turnover.[54,56] Newer techniques using a label-free mass spectrometry-based strategy have been used to distinguish no versus high levels of bone disease.[57] Results from ongoing trials evaluating biomarkers that mirror the dynamics of bone disease in MM will help to identify their true value in clinical practice.

EPIGENETIC BIOMARKERS

There is now substantial evidence supporting the notion that epigenetic changes, including DNA methylation, histone acetylation, and microRNAs, are important for MM development and progression. Normal B cells, plasma cells, and MGUS cells have a methylation pattern that is distinct from that of malignant cells in patients with newly diagnosed MM and plasma cell leukemia.[58] The transition from MM to plasma cell leukemia has been associated with promoter hypermethylation of genes involved in cell signaling and cell adhesion pathways, and with patterns of global hypomethylation.[59,60] Unsupervised clustering of myeloma samples de-

fined several independent methylation profiles of cytogenetic groups; the most distinct of these belonged to the t(4;14) translocation associated with histone methyltransferase activity of MMSET.[61] The importance of miRNAs in the regulation of cell differentiation, survival, and apoptosis was highlighted soon after their discovery and it is now known that aberrant miRNA expression occurs in MM, in which miRNAs can act as oncogenic drivers or tumor suppressors and can also interact closely with other critical epigenetic regulators.[62] Data indicate that MGUS and MM share a common miRNA signature that distinguishes them from normal plasma cells, but MM cells exhibit changes in additional miRNAs compared with MGUS cells. Commonly deregulated miRNAs in MM include miR-21, the miR-17–92 cluster, the miR-15a/16 cluster, and the miR-29 and miR-34 families.[63] Thus, the discovery of epigenetic changes has provided additional insights into the pathogenesis of myeloma.

BIOMARKERS FOR RISK OF PROGRESSION IN MYELOMA PRECURSORS

At present, there are no reliable biologic markers that predict which individuals with MGUS or SMM will progress to MM. In the absence of such markers, patients are risk stratified based on two commonly used models developed by the Mayo Clinic and the Spanish study group that are derived from clinical variables identified through retrospective studies.[64,65] The Mayo Clinic model is based on quantification of M spike and bone marrow plasma cells, whereas the Spanish model includes the degree of clonality assessed by immunophenotyping (i.e., the balance between malignant and residual normal plasma cells). Recent studies indicate that chromosomal abnormalities are also critical determinants of the rate of progression in SMM. Two studies showed that the presence of del(17p) or t(4;14) is associated with the shortest time to progression and that trisomies and gains of 1q21 are risk factors for progression (Table 1).[66,67] Genetic heterogeneity is established early during clonal plasma cell development. GEP has identified major differences between MGUS and normal plasma cells, yet no clear distinctions have emerged between MGUS and MM.[68,69] The Arkansas group used GEP clustering in 351 patients with MM, 44 with MGUS, and 12 with SMM, and identified four major signatures; a MGUS-like signature in patients with MM was associated with improved survival.[70] A recent prospective observational study showed that increased GEP70 score was an independent predictor of risk of progression from precursors to MM.[71] Functional MRI incorporating DCE, diffusion weighting, or PET has the potential to detect small volumes of active tumor before morphologic changes become apparent. In a small study, DCE MRI microvascular parameters represented as rate constant (kep) and transfer constant (ktrans) showed moderate correlation with microvessesl density (MVD) in patients with MGUS, SMM, and MM, whereas MVD increased progressively along the myeloma spectrum, recapitulating an angiogenic switch.[72] The presence of MRI focal lesions is a predictor of early progression. In the largest study to date, involving 149 patients with SMM, focal marrow abnormalities were identified in 28% of subjects and the presence of two or more focal lesions was shown to have independent prognostic significance for progression to symptomatic disease.[73] A recently published trial of longitudinal MRI in untreated SMM patients revealed that MRI-progressive disease, as defined by new or increasing focal or diffuse bone marrow abnormalities, was associated with a 16.5-fold increased risk of progression to MM compared with MRI-stable disease (p < 0.0001).[74] Although further technical refinement is needed, it is likely that biomarkers based on GEP, imaging, and immunophenotyping that can be followed in patients with MGUS or SMM will be introduced into the clinic, allowing us to better understand variations in sequential trajectories and predict those patients who are at high risk of disease progression and for whom treatment intervention is essential to prevent the emergence of serious end-organ damage.

CONSIDERATIONS ON DESIGNING BIOMARKER-FOCUSED CLINICAL TRIALS

Although it is currently feasible to define different risk groups using sets of prognostic biomarkers, we are not yet at the point where this can actually drive go/no-go decisions or support a specific alternative treatment strategy in a high-risk group or less intense therapy for those with favorable risk. Some might argue that this concept of optimization of therapy would not apply for an incurable malignancy, and that all patients should receive the optimal currently available treatment strategies (including ASCT) that have been tested in phase III clinical trials to achieve the best outcome. However, emerging evidence based on use of the best available treatments for newly diagnosed MM and SMM, together with refinements in risk categorization, clearly indicates that many patients have a greater than 50% chance of surviving more than 10 years and may not need up-front intensification of treatment.[75] In contrast to standard-risk patients, for whom progress has been made in improving outcomes, clinical trials based on a 'one-size-fits-all' strategy have in general been disappointing for high-risk MM, which constitutes a distinct subgroup based on clinical and biologic biomarkers (Table 1).[75-77] For this patient population the median survival has remained poor (approximately 2 to 3 years) despite aggressive therapy incorporating almost every available drug and treatment modality. In such cases, treatment intensification with dose-dense chemotherapy that is rotated and maintained for a long period of time to potentially induce consistent therapeutic pressure on the myeloma clone has not yielded encouraging results.[31] An early IFM study compared the efficacy of allogeneic stem cell transplantation and ASCT in high-risk patients defined by high β2-microglobulin and del(13q) detected by FISH.[78] Although the definition of high-risk disease has improved since the inception of this trial, no difference in EFS was seen between the two transplant types. The strategy of tandem ASCT followed by nonmyeloablative allogeneic transplant led to improved CR but did not translate into a survival benefit compared with double ASCT be-

cause of greater treatment-related mortality.[79] Current studies are looking into immune manipulation in the context of allogeneic transplantation. Tumor/stromal interactions, signaling pathway dependencies, and genetic and epigenetic alterations in MM provide novel targets for the development of drugs that are intended to abrogate malignant progression through specific drug protein interactions (Table 2; reviewed in Boyd et al.[80]). Combinations of molecular targeted drugs or monoclonal antibodies and a tolerable conventional chemotherapy regimen seem promising, specifically for high-risk MM. As more effective treatment options become available, it is imperative to refine the yardstick for measuring the depth of responses that correlate with outcome. Once the definition of MRD in MM is standardized, the next generation of randomized studies should include MRD as a surrogate endpoint to assess which therapeutic strategy produces the deepest and most sustainable response.

The ability of high-throughput "omics" platforms to profile a large number of analytes in a single assay, together with the rapid expansion of next-generation sequencing for clinical use, is increasing the technical and logistical complexity of biomarker validation. As a result, biomarkers for identifying high-risk disease will undergo refinements and will need to be validated in order for us to screen an adequate number of patients for clinical trials focused on the subgroup of interest. Steps in the development, validation, and qualification of candidate biomarkers are shown in Fig. 1. The Clinical Laboratory Improvement Amendments (CLIA) approach suggests that the development of biomarkers should be performed in defined laboratories according to relevant standard operating procedures in order to establish consistency in sample handling, sample testing, assay interpretation, and reporting of results across laboratories. This implies that all biomarkers should be developed in CLIA-certified laboratories and in the context of clinical trials in which data are collected according to the principles of good clinical practice.[81] For a biomarker to be used to direct patient care, it must be shown to have clinical utility with very high levels of evi-

TABLE 2. Biomarkers for Molecularly Targeted Therapies in Multiple Myeloma

Alterations/Genes	Target/Biomarker	Prevalence	Prognosis	Targeted Drug
t(4;14) *FGFR3/MMSET*	FGFR3 tyrosine kinase receptor	10-15%	Intermediate	PRO-001, CHIR 258, PKC412
t(14;16) *c-MAF* t(14;20) *MAFB*	MAF overexpression	5-10%	Poor	MEK inhibitors
t(11;14) *CCND1* t(6;14) *CCND3*	Cyclins	19%	Standard	Cyclin D inhibitors
8q24 translocations (*c-MYC*)	c-MYC		Poor	Bromodomain inhibitors e.g., JQ1
+1q (*CKS1B*, *PDZK1* and *BCL9*)	STAT3 and MEK/ERK signaling	39%	Poor	STAT3 and MEK inhibitors
Deletion of 1p (*FAF1* and *CDKN2C*)	-	11%	Poor	
Deletion of 13q (*RB1*)	-	45% by FISH and 19% by conventional cytogenetics	Earlier studies showed poor survival	Mutant RB1 inhibitor
Deletion of 17p (*TP53* and *MDM2*)	Mutant or WT TP53	10%	Poor	Nutlin, PRIMA-1, CHK inhibitors, and filanesib (target G2M)
Proliferative myeloma	Ki67, GEP-PR subtype		Poor	Spindle kinase inhibitors, Aurora kinase inhibitors
NF-κB pathway (multiple genes e.g., *NFKB2*, *NFKB1*, *CYLD*, *TACI*, *NIK*, *TRAF2*, *TRAF3*, *BIRC2*, *BIRC3*, *VWOX*, and *CD40*)	Gene expression signature		Poor	MLN120B (inhibitor of IKKβ)
JAK/STAT pathway (*CCND2*)	Cyclins	50%		JAK inhibitors: atimprimod, AZD1480, TG101209, and INCB16562
MAPK/RAS pathway	*RAS* mutations (20-35%)	20-35% *BRAF* mutations (4%)	Poor	Farnesyl transferase inhibitors: perillic acid, FTI-277, and tipifarnib. MEK inhibitors: AZD6244 and AS703026. BRAF kinase inhibitors
PI3 kinase pathway	Cyclins			PI3K inhibitors: SF1126, pichromene, and CAL-101
				AKT inhibitor: Perifosine
				mTOR inhibitors: Rapamycin, Temsirolimus
Epigenetic changes	Histone methyltransferase activity of MMSET	15%		HDAC6 inhibitor: ACY-1215
				DNA methyltransferase inhibitors e.g., 5-azacytidine, 5-aza-2´deoxycytidine

FIGURE 1. Roadmap for the Identification of Fit, Robust, Valid, and Clinically Useful Biomarkers
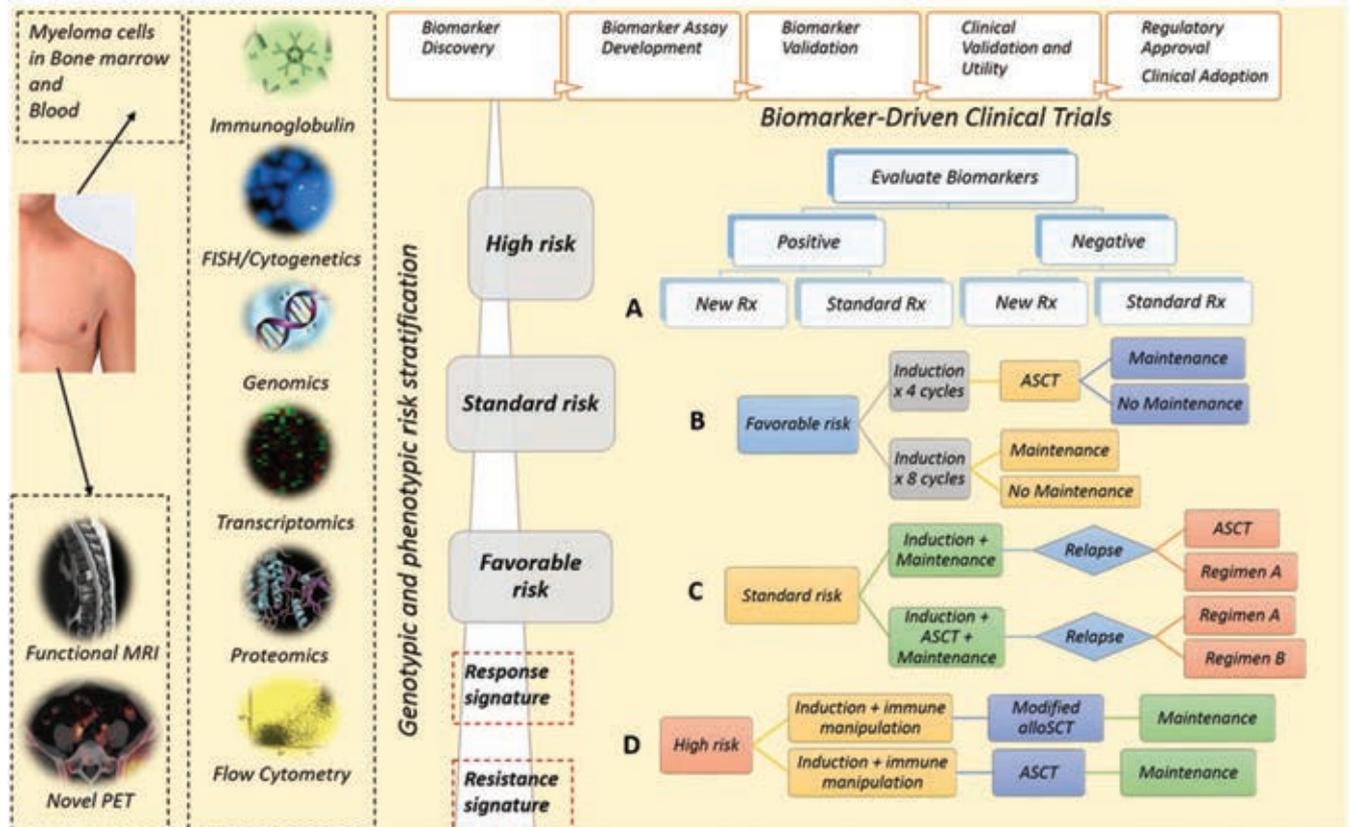
In the future, several new biomarkers will be identified through a "discovery" approach utilizing techniques such as high-throughput sequencing, omics technologies, gene expression arrays, mass spectroscopy, multiplex flow cytometry, and innovative imaging strategies. Several steps must be completed before the marker can be applied in the clinic. First, a cohort of samples is analyzed to determine whether the effects observed in cell assays or animal models are recapitulated in humans. After demonstrating target engagement/modulation, subsequent testing involves analyzing an independent sample cohort to validate the original hypothesis-generating findings, and evaluation to confirm that the new biomarker will provide additional information that is useful for clinical decision-making. These concepts have been termed analytic validity, clinical validity, and clinical utility. Based on the new set of biomarkers, risk stratification schemas and treatment response/resistance signatures are expected to evolve. It will be important to utilize the correct biomarker-focused trial designs to evaluate a biomarker's ability to predict treatment response. Biomarker-stratified designs (A) that aim to evaluate both a new treatment and a biomarker within the same trial by enrolling all-comers to new versus standard treatment with a planned biomarker subset analysis will be more suitable for evaluating biomarkers such as t(4;14). If phase IIb shows a significant interaction of effects in patients with/without t(4;14), the integral selection of only patients with t(4;14) for the confirmatory phase III trial would follow. Development of multibiomarker risk assessment models for clinical applications will require well-designed clinical trials within the framework of carefully selected questions, such as whether maintenance can be omitted for a standard biologic risk group (B), whether up-front autologous transplant is a uniform requirement for all eligible patients (C), and whether the high-risk group can be offered alternative investigational strategies to improve outcome (D).

dence. Clinical utility refers to the ability of the biomarker to improve clinical decision-making and patient outcomes. Whereas a good predictive biomarker indicates who should receive the targeted treatment, a good prognostic biomarker does not necessarily have clinical utility. We already have several risk stratification biomarkers that are prognostic; however, these have not been validated for clinical utility. For example, even if the ISS distinguishes outcomes between three subgroups, clinical evidence supporting de-escalating or escalating treatment according to the risk group is not available. Improvement in patient outcomes can be achieved by conducting strategic clinical trials involving risk models based on multiple biomarkers.

Evaluation of prognostic biomarkers for clinical utility will require carefully designed clinical trials within the framework of carefully asked questions (Fig. 1). Prospective enriched integral biomarker trial designs that predefine an eligible population by the presence of a strong biomarker (i.e., HER2 in breast cancer or BCR-ABL in CML) may not be

appropriate for testing a new treatment in patients with MM as positive results from such a study would leave one wondering whether the treatment might also have worked in the biomarker-negative subgroup. Moreover, selecting patients with, for example, BRAF-mutated tumors (which have a 4% incidence within MM) for anti-BRAF therapy presents a difficult challenge. Such a phase III trial would require screening of thousands of patients with MM to accomplish a BRAF-mutated phase III selection. Moreover, if we are to generate high-quality data supporting the magnitude of benefit of a biomarker for a patient, clinician, or third party payer, it is important to evaluate and report biomarker-focused clinical trials within the framework of defined guidelines such as REMARK (Reporting Recommendations for Tumor Marker Prognostic Studies) to ensure that all necessary information is included.[82]

The presence of clonal heterogeneity and subclonal evolution within a single patient across time (with treatment) and space (within medullary and extramedullary sites) has im-

portant implications for the development of biomarkers. In the future, characterization of the size of the subclone carrying the target will very likely influence the choice of treatment because completely eradicating a clone that is present 90% of the time would be much more important than targeting a clone that is present only 5% of the time.[81] In this regard, samples should be prospectively collected from large clinical trials, not only at the time of diagnosis but also longitudinally, for the creation of repositories to either validate existing prognostic markers/signatures or generate new ones. Several ongoing multinational efforts, such as the CoMMpass study, aim to provide a comprehensive understanding of MM in the era of novel agents.

CONCLUDING REMARKS

Studies performed over the last few years have emphasized that MM is a complex disease that is not amenable to treatment through a single therapeutic approach or inhibition of a single target or single pathway. A new generation of biomarkers based on cytogenetics, epigenetics, focal lesions, clone status, and GEP signature is beginning to provide clinicians with more information about the clinical behavior of the disease, providing a basis on which risk stratification models and therapies can be continuously refined. The new biomarker-based definition of MM has direct clinical implications for initiating treatment in a biomarker-positive subgroup. Further studies should apply risk stratification in the trial design to specifically answer questions regarding treatment within each risk group. Currently, few data are available to support the use of biomarker-guided treatment optimization, although with a robust pipeline of novel targeted agents and standardized definitions of MRD linked to traditional clinical endpoints, this remains an important goal of ongoing research. A systems-based approach including collaboration across multiple institutions and investigators will enhance our ability to conduct biomarker-focused clinical trials in a more effective manner.

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Multiple Myeloma: From Front-Line to Relapsed Therapies

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OVERVIEW

Recent developments in the treatment of multiple myeloma (MM) have led to improvements in response rates and to increased survival. A major advance in the last decade has been the introduction of the novel agents thalidomide, bortezomib, and lenalidomide as part of front-line treatment in both the transplant and nontransplant settings. However, disease relapse is inevitable for the majority of patients and myeloma typically recurs more aggressively with each relapse, eventually leading to the development of treatment-refractory disease. Several phase II and III trials have demonstrated the efficacy of recently approved agents in the setting of relapsed and relapsed and refractory MM, including pomalidomide and carfilzomib. Ixazomib, an oral proteasome inhibitor, and multiple other novel classes of agents are being investigated. These include monoclonal antibodies and histone deacetylase inhibitors, which may further add to the therapeutic armamentarium for this malignancy. Therefore, in a disease characterized by multiple relapses, the optimal sequencing of the different effective options is an important consideration in attempting to prolong survival.

Multiple myeloma accounts for 1.5% of all cancers and approximately 13% of all hematologic malignancies.[1] Approximately 86,000 new cases of MM occur annually worldwide. In the United States, 24,050 new cases were estimated for 2014 (age-standardized rate of 5.9 per 100,000) with MM accounting for 11,090 deaths.[2] In Europe, there were an estimated 17,935 new cases in 2012, with an age-standardized rate of 5.5 per 100,000, and 10,390 deaths because of MM.[3] This malignant neoplasm primarily affects older individuals with a median age at the time of diagnosis of about age 70.[4]

The median survival of patients with MM has improved substantially over the past decade, from 3 to 4 years to approximately 7 to 8 years,[5] a development due to the establishment of high-dose therapy followed by autologous stem cell transplantation (HDT-ASCT) as a routine procedure; significant improvements in supportive care strategies; and the introduction and widespread use of novel agents, including the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide, and the proteasome inhibitor (PI) bortezomib. These agents now form the basis of many current standard-of-care approaches for first-line therapy in the transplant and nontransplant settings, and for the treatment of relapsed disease. Active research into new therapies has resulted in the development of additional novel agents, some of which are now approved for relapsed/refractory MM. These include the next-generation IMiD pomalidomide, which was approved in the United States and Europe in 2013, and the PI carfilzomib, which was approved in the United States in July 2012. Ixazomib, an oral PI, and multiple other novel classes of

agents, such as monoclonal antibodies and histone deacetylase (HDAC) inhibitors, currently are being investigated. These agents will further add to the therapeutic armamentarium and possibly increase the number of lines of therapy that patients will receive during the course of their disease treatment.[6] The optimal sequence of combination therapies from the time of diagnosis to the time of the most advanced phase of myeloma has to be considered carefully to minimize resistance and toxicity, and to improve quality of life (QOL), the treatment-free interval (TFI), and, most importantly, overall survival (OS).

FRONT-LINE TREATMENT IN YOUNG PATIENTS: ASCT IS THE STANDARD OF CARE

For young patients, who generally are considered to be those younger than age 65 to 70 and without prohibitive comorbidities, HDT-ASCT is the treatment of choice in newly diagnosed MM. This is based on a number of randomized studies conducted in the 1990s, which showed that intensive therapy with ASCT improved survival over conventional chemotherapy.[7] In the last decade, the introduction of the novel agents thalidomide, bortezomib, and lenalidomide into the front-line setting has markedly improved the rate of complete remission (CR) that can be achieved both before and after ASCT without substantially increasing toxicity. This has important implications because the achievement of high-quality responses is a significant prognostic factor for outcome.[4,7-8] Based on a number of trials investigating different combinations of agents as induction reg-

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imens,[4,6,9] the 2015 recommendation is the use of a three-drug regimen based on bortezomib/dexamethasone, with the third agent cyclophosphamide, adriamycin, thalidomide, or lenalidomide.[4,10]

Novel agents also have been included in the post-ASCT setting. Their incorporation into consolidation therapy[11] has resulted in the achievement of deep molecular- or flow cytometry– defined complete responses, with some patients remaining alive and free of disease, with a minimal residual disease (MRD) negativity, which are vital prerequisites for extended disease-free survival.[12] These unprecedented results were only possible previously with allogeneic transplantation (alloSCT), the routine use of which is not recommended outside clinical trials in MM because of excessive transplant-related mortality.[13] Recent data also show that maintenance following HDT may dramatically increase progression-free survival (PFS) by almost 2 years.[14] The implementation of an optimal strategy, consisting of novel agent-based induction, HDT, and the use of novel agents in consolidation and maintenance, may result in a 5-year survival rate of 80%, which is unprecedented. Moreover, a subset of patients who present with good prognostic features at the time of diagnosis might be considered cured.[15-16] However, the strategy of optimized induction, HDT, and ASCT followed by PI- and/or IMiD-based consolidation and maintenance is currently restricted to clinical trials.

The high efficacy of novel agents has resulted in questioning of the role of up-front ASCT. A number of studies have been initiated to investigate these agents up front without ASCT. In a nonrandomized phase II trial of RVD (lenalidomide, bortezomib, dexamethasone) in the up-front setting, no difference in outcome was seen for patients undergoing HDT or not.[17] Impressive results, including high rates of MRD-negative responses, also have been reported for the combination of carfilzomib/lenalidomide and low-dose dexamethasone (KRd) without up-front ASCT in another phase II study.[18] Based on these results, some physicians are considering that delaying ASCT to the time of the first disease relapse could be an attractive option. In 2015, only limited data from randomized studies are available to address the issue of early versus late ASCT. However, preliminary results favor early ASCT plus novel agents over novel agents alone. The first prospective study comparing conventional chemotherapy plus novel agents to tandem ASCT in newly diagnosed MM patients is being conducted by the Italian myeloma group and was recently reported by Palumbo et al.[19] Patients received lenalidomide/dexamethasone (Rd) induction and then were randomly assigned to melphalan/prednisone/lenalidomide (MPR) or tandem ASCT. Both PFS and OS were substantially longer with high-dose melphalan plus ASCT than with MPR (median PFS, 43.0 vs. 22.4 months; and 4-year OS, 81.6 vs. 65.3%). Two other ongoing trials, one conducted by the European Myeloma Network (EMN02 study, NCT01208766) and another by the IFM in conjunction with a U.S. consortium (IFM/DFCI 2009 study, NCT01208662) are investigating the same question and have enrolled 1,500 and 1,000 patients, respectively. Although variability in consolidation and maintenance strategies may affect PFS when comparing early versus

late transplant approaches, these two studies will solve many issues regarding the role of systematic front-line ASCT in the treatment of young patients eligible for HDT. Results, however, are not expected before the end of 2015.

FRONT-LINE TREATMENT OF PATIENTS NOT ELIGIBLE FOR ASCT

Since the introduction of thalidomide, bortezomib, and lenalidomide, the median OS in older newly diagnosed multiple myeloma (NDMM) patients has increased from approximately 30 to 60 months.[5,20] Several regimens that include one or two of these novel agents have been explored. The combination of melphalan/prednisone/thalidomide (MPT) is a standard option for NDMM patients who are not candidates for ASCT.[4,10,21-22] The addition of thalidomide to melphalan/prednisone (MP) was shown to delay disease progression in several randomized trials and to improve OS in some patients.[4,21] A meta-analysis of published data from six randomized trials confirmed an improvement in PFS and OS with MPT compared to MP.[22] The reported median PFS and OS with MPT were 20.3 and 39.3 months, respectively.

The combination of bortezomib/melphalan/prednisone (VMP) is another well-established standard of care. This regimen initially consisted of 2 times a week intravenous administration of bortezomib, based on the phase III VISTA trial,[23] which showed that VMP was superior to MP across all efficacy endpoints, including response rate, CR rate, median time to progression (TTP, 24 vs. 16.6 months) and OS. Based on clinical data published in 2010, bortezomib use evolved from 2 times a week to 1 time a week,[24] and from 2012, the subcutaneous route of administration has found increasing use over the intravenous route based on data demonstrating improved tolerability for this mode of administration.[25] The final analysis of the VISTA trial after a median follow-up of 60 months confirmed the superiority of VMP versus MP in terms of median time to second-line antimyeloma therapy (31 vs. 20.5 months) and median OS (56 vs. 43 months).[26] Bortezomib/dexamethasone (VD) and bortezomib/thalidomide/dexamethasone (VTD) have yielded similar results in the up-front setting in nontransplant eligible patients.[27]

Lenalidomide mainly has been used in combination with MP (MPR),[28] or with low-dose dexamethasone (Rd).[29,30] For the MPR regimen, tolerability was found to be reduced in patients over age 75, and the combination also has been associated with an increased incidence of second primary hematologic malignancies.[28] In the recent phase III FIRST study, which included 1,623 transplant-ineligible patients, the continuous Rd regimen administered until disease progression, intolerance, or for a fixed duration of 18 cycles (72 weeks; Rd18) was compared to MPT administered for 12 cycles (72 weeks). Continuous Rd substantially extended PFS and OS compared to MPT. With a median follow-up of 37 months, the median PFS was 25.5 months for Rd, compared to 20.7 months for Rd18 and 21.2 months for MPT. The 4-year estimated OS was 59% for Rd, 56% for Rd18, and 51% for MPT. In addition, Rd was superior to MPT across all

other efficacy endpoints, including response rate, TTP, time to treatment failure, time to second-line antimyeloma therapy, and duration of response (DOR). Rd also was generally better tolerated than MPT.[30]

The current standard regimens MPT and VMP are based on melphalan and are administered for a fixed duration (9 to 12 cycles).[4] The alkylator-free doublet regimen Rd, delivered as a continuous therapy, has demonstrated superiority over MPT,[30] and continuous Rd will likely become a new standard of care for transplant-ineligible patients with NDMM. This represents a dual paradigm change in a disease in which alkylating agents and fixed-duration therapy have been standard for decades. We anticipate that the two most important front-line therapeutic options in 2015 and 2016 probably will comprise either VMP or Rd.

RELAPSED MULTIPLE MYELOMA AFTER ASCT

Four general approaches to the management of symptomatic disease relapse following initial ASCT may be considered: (1) reinduction followed by salvage ASCT, (2) reinduction followed by alloSCT, (3) reinduction with continuation of conventional chemotherapy using rational combinations of novel therapies for relapsed/refractory disease, and (4) participation in clinical trials to evaluate any of the first three possibilities. Currently, only limited comparative data are available to support one approach over another.[31]

REINDUCTION FOLLOWED BY SALVAGE ASCT

No guidelines on the optimal salvage regimen exist. The choice of the reinduction regimen typically depends on patients' responses to the initial induction therapy; comorbidities, such as persistent peripheral neuropathy (PN) related to prior bortezomib; burden of disease; or patients whose disease relapsed on maintenance lenalidomide and/or bortezomib.[31-32] Triplet reinduction regimens commonly are used. In case of prolonged TFI following front-line ASCT, it is reasonable to consider using the same combination regimen that was used as the initial induction therapy, such as VCD, VTD, or RVD. Patients who will benefit most from salvage ASCT are those with chemotherapy-sensitive disease at relapse and those with a long duration of response to the initial ASCT.[31-33] On average, the PFS benefit following a salvage transplant is approximately one-half that of the PFS after the first transplant. Salvage ASCT may not be recommended if the time to relapse following the first ASCT is less than 18 to 24 months.[31-33] Whether salvage ASCT yields better outcomes than salvage chemotherapy is not conclusively known. Retrospective and uncontrolled data have suggested a possible trend toward improved survival with salvage transplant versus salvage combination chemotherapy.[31] A recent multicenter randomized phase III study compared salvage ASCT to cyclophosphamide single-agent administered for 12 weeks.[34] Patients were eligible if their disease had progressed or relapsed at least 18 months after the initial ASCT. All patients received re-induction with the PAD (bortezomib, doxorubicinm dexamethasone) regimen and were randomly assigned to either ASCT or cyclophosphamide. Although the median time to progression was substantialy longer for patients undergoing ASCT (19 vs. 11 months), the OS did not differ between the two arms. Many experts considered the cyclophosphamide arm of this trial to be suboptimal. Since salvage regimens that are more effective than single-agent cyclophosphamide are now available, additional prospective randomized trials comparing novel triplet combination therapies to salvage ASCT are needed.

REINDUCTION FOLLOWED BY SALVAGE ALLOASCT

Reduced-intensity conditioning alloSCT in the salvage setting sometimes is considered an appropriate option for younger patients with good performance status and high-risk features, including adverse cytogenetics, a high-risk gene expression profile, high LDH, or plasma cell leukemia. No prospective randomized studies comparing salvage alloSCT to salvage ASCT are available. Some retrospective analyses comparing these two approaches have been reported; they show a higher nonrelapse mortality rate with alloSCT, and PFS/OS rates in salvage ASCT.[31] A limited number of studies with few patients have evaluated salvage alloSCT versus no alloSCT. These studies have shown improved PFS for patients undergoing salvage alloSCT but without an OS benefit.[31] As the number of effective regimens for relapsed MM continues to increase, the use of salvage alloSCT should be restricted to clinical trials.[13,31]

SALVAGE CHEMOTHERAPY AND CLINICAL TRIALS

Numerous options exist for relapsed disease and the number of effective and available agents and combinations is increasing rapidly (Table 1). Only one trial has prospectively compared two- versus three-drug combinations in patients whose disease relapsed following front-line ASCT. Garderet et al demonstrated that the triplet combination of VTD was associated with a higher response rate, a longer time to progression (18.3 vs. 13.6 months), and a trend toward improved OS. However, VTD also was associated with a higher incidence of grade 3/4 toxicities as compared to thalidomide/dexamethasone.[35]

Two other recent prospective phase III trials have confirmed that triplet combinations are superior to doublets. However, these studies enrolled not only young, but also older patients. All had received one to three prior lines of treatment, and only a part of the patients were treated with front-line ASCT. In the PANORAMA-1 study, which compared VD-placebo versus VD plus the HDAC inhibitor panobinostat, 58% of the patients were younger than age 65, 56% had received a previous ASCT, and 51% were treated at the time of their first disease relapse.[36] Overall, the median PFS was substantially longer in the panobinostat group than in the placebo group (12 vs. 8 months; hazard ratio [HR] 0.63). This benefit was observed across the subgroups of patients younger than age 65 (HR 0.59), those who were treated for their first disease relapse (HR 0.66), and those previously treated with ASCT (HR 0.64). Of note, this triplet combi-

TABLE 1. Recent and Ongoing Phase III Trials in Relapsed Multiple Myeloma: Two- versus Three-Drug Combinations

	No. of Patients	ORR ($>$ PR) (%)	Median PFS (mo)	OS
IFM 2005-04/MMVAR[35]				
TD	134	72	13.6	24 mo, 65%
VTD	135	88	18.3, p = 0.001	71%, p = 0.09
PANORAMA 1[36]				
VD	387	54.6	8.08	Median 30.4
VD-Panobinostat	381	60.7, p = 0.09	11.99, p $<$ 0.0001	33.6, p = 0.26
MM007 (NCT 01734928)				
VD	NA	NA	NA	NA
VD-Pomalidomide				
ASPIRE[37]				
Rd	396	66.7	17.6	24 mo, 65%
Rd-Carfilzomib	396	87.1, p $<$ 0.001	26.3, p = 0.0001	73.3%, p = 0.04
ELOQUENT-2 (NCT01239797)				
Rd	NA	NA	NA	NA
Rd-Elotuzumab				
POLLUX-MMY3003 (NCT02076009)	NA	NA	NA	NA
Rd				
Rd-Daratumumab				
TOURMALINE-1 (NCT61564537)	NA	NA	NA	NA
Rd				
Rd-Ixazomib				

Abbreviations: ORR: overall response rate, PR: partial response; PFS: progression-free survival; mo, months; OS: overall survival; TD: thalidomide-dexamethasone; VTD: bortezomib-thalidomide-dexamethasone; VD: bortezomib-dexamethasone; Rd: lenalidomide-dexamethasone; NA, not available.

nation was associated with more gastrointestinal toxicities, thrombocytopenia, and fatigue compared to VD. In the second recently reported phase III ASPIRE study, in which Rd was prospectively compared to Rd-carfilzomib, 43% of the patients were treated in first relapse of disease, whereas 56% had received a prior transplant.[37] This trial showed that the addition of intravenous carfilzomib to Rd resulted in a substantially improved PFS (median, 26.3 vs. 17.6 months in the control group); this was observed across all predefined subgroups. Rd-carfilzomib had a favorable risk-benefit profile and patients in the carfilzomib group reported a superior health-related QOL.

Triplet combinations at first relapse probably will become standard in the near future, but the benefit in terms of overall response rate (ORR) and PFS will have to be balanced with cost and toxicity. Overall survival as a secondary endpoint also is important. In the setting of relapsed disease, the results of ongoing trials investigating other classes of agents, such as the monoclonal antibodies, are eagerly awaited. Although elotuzumab, which targets SLAMF7, lacks activity as a single agent in relapsed myeloma, an ORR of 82% and more than 30 months PFS was reported when this agent was combined with Rd in a phase II trial.[38] These results were the basis of the ongoing ELOQUENT-2 trial that is prospectively comparing Rd versus Rd-elotuzumab in patients whose disease had relapsed. The same design also was selected for the prospective comparison of Rd versus Rd-daratumumab in the ongoing

phase III randomized trial POLLUX. Daratumumab, a monoclonal antibody targeting CD38, has shown impressive activity as a single agent in patients with advanced disease[39] and in combination with Rd in phase II trials.[40] Another monoclonal antibody targeting CD38, SAR650984, currently is also being developed in relapsed disease.[41] A further phase III trial using Rd as a control arm could change the treatment landscape of relapsed myeloma. The placebo-controlled TOURMALINE-MM1 study is currently comparing Rd versus Rd-ixazomib in patients with relapsed disease. This combination also was tested along with Rd as front-line treatment in a phase II study resulting in impressive response rates.[42] The all-oral triplet combination Rd-ixazomib could become a convenient rescue treatment, provided that toxicity in relapse is similar to that observed in the front-line setting. VD is, as mentioned above, another backbone regimen in relapsed myeloma, and this combination also is currently being compared to VD plus pomalidomide in a prospective phase III international trial.

RELAPSED MULTIPLE MYELOMA IN PATIENTS NOT PREVIOUSLY TREATED WITH ASCT

As discussed previously, the front-line treatment of older patients in 2015/2016 consists of VMP, Rd, and, to a lesser extent, MPT. If their disease relapses, patients may either repeat the initial therapy—if this treatment had a fixed duration and

was able to induce a long TFI— or switch to a different treatment regimen. Several factors influence this decision, including drug availability in the specific country, patient age, comorbidities, performance status, prior treatment, duration of remission to the front-line regimen, and initial toxicities. Although anti-MM treatments have proven efficacious in older patients with relapsed MM, their use is often associated with substantial adverse effects that can affect treatment choice. As such, older and frail patients usually are treated with mild, low-dose regimens, typically thalidomide or bortezomib combined with either melphalan/prednisone or cyclophosphamide/dexamethasone.

RELAPSE FOLLOWING INITIAL VMP

For patients previously exposed to a PI plus an alkylator, Rd is the preferred option; it is approved, administered orally, and easily manageable. As described above, the results of ASPIRE (carfilzomib-Rd), POLLUX (daratumumab-Rd), Eloquent-2 (elotuzumab-Rd), and TOURMALINE-MM1 (ixazomib-Rd) will soon modify the landscape of relapse therapies. The choice of the particular regimen will depend on safety, duration of response, OS rates, and cost. The population of older patients is a very heterogeneous group, and the studies described above generally have selected a fit population of patients, excluding frail patients, for whom QOL is a major issue. In early 2015, only the results of the ASPIRE study are available as a full manuscript and the PFS benefit was described in patients older than age 65 (HR 0.85).

RELAPSE FOLLOWING MPT

For patients treated up front with a combination of an alkylator and thalidomide, several possibilities at the time of first disease relapse exist. Rd is one possibility. A bortezomib-based approach also is possible if patients did not experience PN with thalidomide. Bortezomib/dexamethasone and bortezomib/liposomal doxorubicin are two approved options. The first is the preferred option because of convenience and reduced toxicity. The triplet combination of RVD also was tested in first disease relapse in a phase II study with good results.[43] Similarly, the combination of bortezomib/dexamethasone plus bendamustine has proven to be effective in phase II studies.[44] Other triplet combinations currently undergoing evaluation in phase III trials could present future options, such as panobinostat plus bortezomib and dexamethasone following the PANORAMA-1 results, or pomalidomide plus VD.

RELAPSE FOLLOWING RD

The FIRST trial demonstrated the superiority of continuous Rd over MPT in terms of ORR, PFS, and OS. When approved, Rd will be a well-tolerated and effective oral front-line regimen. At the time of progression on Rd, the addition

of a third drug will not be the preferred option. Instead, the combination of a PI plus/minus alkylator (VD, VCD, or VMP) could be the best choice. Depending on approval, the triplet VD/panobinostat or VD/pomalidomide also could be proposed.

TREATMENT OF RELAPSED AND REFRACTORY MULTIPLE MYELOMA

Relapsed-and-refractory disease is defined as a minimal response to salvage therapy, as disease progressing during salvage therapy, or disease progressing within 60 days of the last therapy. These patients present a challenge because they are likely to have a more aggressive disease and to be heavily pretreated, thus having more pre-existing toxicities. Clinical trials remain an important option for these patients.

Depending on the treatment to which a patient is refractory, thalidomide, lenalidomide, or bortezomib (as single agents or in combination) can be used for the subsequent line of treatment. However, response rates tend to be lower than in patients whose MM had relapsed because of the more advanced state and aggressive nature of the disease and the development of treatment resistance. Patients whose disease is refractory to bortezomib and an IMiD have a median survival of only 9 months with salvage treatment.[45] Therefore, there is an unmet need for additional treatments for patients whose disease is refractory to current regimens.

Two agents, pomalidomide and carfilzomib, recently have been approved for use in patients with relapsed and refractory MM, who have failed bortezomib- and lenalidomide-based therapy.

POMALIDOMIDE

In the pivotal phase I/II study MM-002, the combination of pomalidomide with low-dose dexamethasone (Pd) was found to be more efficacious than single-agent pomalidomide in patients with relapsed and refractory MM (ORR, 34 and 15%, respectively).[46] In a randomized phase III study (MM-003), Pd was compared to high-dose dexamethasone in patients with primary refractory or relapsed and refractory MM. At 10 months' median follow-up, the PFS was substantially longer in patients treated with Pd versus patients treated with high-dose dexamethasone alone (median PFS, 4.0 vs. 1.9 months, respectively).[47] Comparable results were seen in a subgroup analysis of patients who were dual-refractory to bortezomib and lenalidomide (74% of patients in the MM-003 trial) (median PFS, 3.7 months).[47] A substantial improvement in OS was observed in the final analysis (median OS, 12.7 vs. 8.1 months).[47]

Pomalidomide in combination with low-dose dexamethasone has been approved in Europe and the United States for patients with relapsed and refractory MM whose disease has progressed following at least two prior therapies, including lenalidomide and bortezomib. As discussed previously, ongoing studies are examining pomalidomide in combination

with other anti-MM treatments and its use in earlier lines of treatment.[32]

CARFILZOMIB

Carfilzomib initially was evaluated in patients with very advanced MM. In the single-arm phase II study PX-171-003-A1, the treatment of patients with relapsed and refractory MM with single-agent carfilzomib led to durable responses, resulting in an ORR of 23.7%, a median DOR of 7.8 months, and a median OS of 15.6 months.[48] Furthermore, the phase II study PX-171-004 examined carfilzomib in patients with relapsed and/or refractory MM who were treated previously with bortezomib and in patients who were bortezomib-naive.[49,50] In patients previously treated with bortezomib, the ORR was 17.1%, with a median DOR of more than10.6 months and a median TTP of 4.6 months,[50] whereas in 126 response-evaluable bortezomib-naive patients, an ORR of 47.6% and a median TTP of 12.0 months were seen.[49] The lower ORR in patients previously treated with bortezomib may be attributable to a subset of patients who developed resistance to the class of PIs.

Both the PX-171-003-A1 and PX-171-004 trials examined a target dose of 27 mg/m^2 of carfilzomib. Higher doses of carfilzomib have been examined in phase Ib/II studies and appear to be associated with an increased likelihood of achieving a clinical response.[32] However, this requires confirmation in further trials. Thus far, doses higher than those recommended in the label have not been examined in patients with relapsed and refractory disease.

CONCLUSION

The tremendously active research into treatments for MM has resulted in a number of highly active new agents and encourages optimism to the goal of transforming MM into a chronic disease. Although none of the agents with novel mechanisms of action (those following the PIs or IMiDs) are yet to be approved, it is reasonable to believe that several will be in the near future. Our task will be to define the optimal sequence of treatment, the optimal combinations both for front-line and relapsed myeloma, according to age, comorbidities, cost, drug availability, and patients' choice.

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LYMPHOMA AND PLASMA CELL DISORDERS

Progress and Challenges in Chronic Lymphocytic Leukemia

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Management of Chronic Lymphocytic Leukemia

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OVERVIEW

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL) is usually diagnosed in asymptomatic patients with early-stage disease. The standard management approach is careful observation, irrespective of risk factors unless patients meet the International Workshop on CLL (IWCLL) criteria for "active disease," which requires treatment. The initial standard therapy for most patients combines an anti-CD20 antibody (such as rituximab, ofatumumab, or obinutuzumab) with chemotherapy (fludarabine/cyclophosphamide [FC], bendamustine, or chlorambucil) depending on multiple factors including the physical fitness of the patient. However, patients with very high-risk CLL because of a 17p13 deletion (17p-) with or without mutation of *TP53* (17p-/*TP53*mut) have poor responses to chemoimmunotherapy and require alternative treatment regimens containing B-cell receptor (BCR) signaling pathway inhibitors. The BCR signaling pathway inhibitors (ibrutinib targeting Bruton's tyrosine kinase [BTK] and idelalisib targeting phosphatidyl-inositol 3-kinase delta [PI3K-delta], respectively) are currently approved for the treatment of relapsed/refractory CLL and all patients with 17p- (ibrutinib), and in combination with rituximab for relapsed/refractory patients (idelalisib). These agents offer great efficacy, even in chemotherapy refractory CLL, with increased tolerability, safety, and survival. Ongoing studies aim to determine the best therapy combinations with the goal of achieving long-term disease control and the possibility of developing a curative regimen for some patients. CLL is associated with a wide range of infectious, autoimmune, and malignant complications. These complications result in considerable morbidity and mortality that can be minimized by early detection and aggressive management. This active monitoring requires ongoing patient education, provider vigilance, and a team approach to patient care.

Chronic lymphocytic leukemia/small lymphocytic lymphoma is the most prevalent lymphoid malignancy in many parts of the world, and approximately 90% of patients are diagnosed with asymptomatic, early-intermediate stage (Rai 0-I, Binet A) disease.[1-3] Many of these patients have indolent disease and could have a normal life expectancy, whereas others have rapid disease progression and poor outcome. There is no proven survival benefit from early therapy in patients with CLL.[4,5] There are now multiple prognostic factors that can be used to predict the risk of disease progression including serum thymidine kinase (TK) and beta-2-microglobulin (β2MG) levels, genomic aberrations assessed by fluorescence in situ hybridization (FISH), ZAP70, CD38, and CD49 expression, somatic hypermutation of the immunoglobulin heavy chain variable region genes (*IGHV*), and mutations of other genes, most prominently *TP53*.[6,7] Despite multiple published studies of these prognostic factors in early-stage CLL, none have been prospectively validated.[8-14] Moreover, there is currently no evidence that early, risk factor–guided intervention with chemoimmunotherapy can alter the natural course of early-stage CLL.[4,5] Therefore, "watch and wait" remains the standard of care for patients with early-stage, asymptomatic CLL. The intervals of monitoring can be adjusted to a patient's risk profile, that is, with 3-monthly follow-up for patients with high-risk markers such as 17p- with or without *TP53*mut, unmutated *IGHV*, 11q22.3 deletion (11q-), and high β2MG or TK serum levels.

INITIAL MANAGEMENT OF CLL
Early-Stage Asymptomatic Patients

A small proportion of patients with early-stage CLL (approximately 3% to 5%) have 17p-/*TP53*mut,[15] which predicts a very high risk of disease progression[16-21] based on data from chemoimmunotherapy studies in patients who required treatment (discussed later). However, a small proportion of early-stage patients with 17p-/*TP53*mut CLL do not have early disease progression,[15,22] and 17p-/*TP53*mut at diagnosis in a patient who does not have active disease[1] is not an indication for treatment. However, these patients deserve a more extensive prognostic work-up and closer monitoring, including the discussion of allogeneic stem cell transplantation (ASCT) as an option in young/fit patients when their disease progresses and treatment is indicated. In summary, outside of clinical trials, the decision to start therapy requires the presence of active disease and is not modified by the presence of any high-risk marker. Prognostic markers can, however, be very helpful in counseling patients and planning patient follow-up.

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Up-Front Management of Advanced Stage, Symptomatic Patients with an Indication for Treatment

Conventional chemoimmunotherapy regimens. The current up-front standard of care in physically fit patients with CLL who require treatment based on IWCLL criteria[1] is fludarabine, cyclophosphamide, and rituximab (FCR; Fig. 1).[17,18,23] This is based on high response rates (40% to 50% complete response [CR]), prolongation of median progression-free survival (PFS), and, notably, median overall survival (OS) compared with FC. However, many patients with CLL cannot tolerate FCR because of age (e.g., age > 65 to 70), decreased fitness (e.g., Cumulative Illness Rating Scale [CIRS] score > 6) and decreased renal function (e.g., creatinine clearance < 30 to 50 mL/min). In these patients, recent trials have suggested that other regimens could be more tolerable.

The German CLL Study Group (GCLLSG) CLL10 study compared FCR versus bendamustine/rituximab (BR) among fit (CIRS ≤ 6, creatinine clearance ≥ 70 mL/min) patients without 17p-, and showed that overall BR was inferior to FCR in terms of response rate and PFS.[24] However, FCR was associated with markedly increased toxicity without substantially better outcomes in patients over age 65, suggesting that BR is a reasonable alternative treatment for this population.

There are now new monoclonal antibody–based treatment options for patients who are not considered fit for FCR-type

KEY POINTS

- Careful observation for disease progression and complications, together with appropriate preventative interventions, remains the standard of care for patients with early-stage, asymptomatic, chronic lymphocytic leukemia. Patients with very high-risk chronic lymphocytic leukemia should not receive treatment until they meet standard criteria for progressive disease.
- The most critical determinants of treatment choice are the presence of 17p-/*TP53*mut, physical fitness/age, and duration of prior response in patients who have received previous treatment. In addition, 17p-/*TP53*mut analysis should be repeated before initiation of therapy.
- The combination of anti-CD20 antibody (rituximab, ofatumumab, or obinutuzumab) and chemotherapy (FC, bendamustine, or chlorambucil) is the standard up-front treatment for the majority of patients with chronic lymphocytic leukemia, with the specific choice of agents mostly determined by fitness of the patient. Based on the dramatic efficacy and favorable toxicity profile of the BCR and BCL2 inhibitors compared with historic chemoimmunotherapy regimens, these agents are the preferred treatment approach for very high-risk chronic lymphocytic leukemia (17p-/*TP53*mut and early relapse).
- Ongoing and future clinical trials are essential to further improve treatment efficacy, determine treatment duration, and eventually develop curative therapy.
- The role of allogeneic stem cell transplant in the management of chronic lymphocytic leukemia requires careful and early discussion in patients who are very high-risk.

treatment. Ofatumumab in combination with bendamustine or chlorambucil was licensed based on the randomized, phase III COMPLEMENT-1 trial that compared chlorambucil with ofatumumab/chlorambucil and showed substantially higher efficacy with only moderately increased toxicity for the combination therapy.[25] The phase III CLL11 trial compared chlorambucil, rituximab/chlorambucil, and obinutuzumab/chlorambucil in a three-arm design. Obinutuzumab/chlorambucil showed higher efficacy compared with both chlorambucil and rituximab/chlorambucil with an acceptable safety profile, which led to the approval of obinutuzumab/chlorambucil for the up-front treatment of patients with CLL who are less fit.[26] Therefore, the combination of anti-CD20 antibody (rituximab, ofatumumab, or obinutuzumab) and chemotherapy (FC, bendamustine, or chlorambucil) is the standard up-front treatment for the vast majority of patients with CLL.

Initial therapy of patients with 17P-/*TP53*mut. Patients with 17p-/*TP53*mut CLL have markedly inferior outcomes with both chemotherapy and chemoimmunotherapy.[6,16,18,19,27] In the subset of patients with 17p- CLL enrolled in the randomized CLL8 study that compared FC with FCR, FCR was superior in terms of overall response rate (ORR, 68% for FCR vs. 34% for FC; p = 0.03) and PFS (median 11.3 months for FCR vs. 6.5 months for FC; p = 0.02), but there was no difference in complete remission rates (CRR, 5% for FCR vs. 0% for FC) or 3-year OS (38% for FCR vs. 37% for FC).[18,27] *TP53*mut and 17p- were the two markers that had the strongest independent effect on PFS and OS in a multivariable analysis after FC and FCR treatment.[27] These unacceptable outcome data were clearly inferior to all other disease subgroups. In the British CLL4 trial, *TP53* mutation was identified as an adverse prognostic marker after treatment with chlorambucil, fludarabine, and FC.[19] These findings of inferior response and poor prognosis are supported by the reported results for 17p- patients undergoing initial treatment of active CLL in studies conducted by MD Anderson Cancer Center/Mayo Clinic,[22] the Spanish Group for CLL,[28] and the Memorial Sloan Kettering Cancer Center[29] which showed that only about 25% of patients with 17p- CLL achieve remissions of 3 years or longer after treatment with purine analog–containing chemoimmunotherapy.

There is limited data on bendamustine containing chemoimmunotherapy for the first-line treatment of patients CLL with 17p-. The GCLLSG CLL2M phase II study of front-line BR enrolled only eight patients with 17p- CLL, of which three responded; all responses were partial, and the median PFS was only 7.9 months.[30] Therefore, BR is likely inferior to FCR as initial therapy in 17p- CLL. In the relapsed/refractory setting, both FCR and BR were unsatisfactory, with response rates of 35% and 7%, respectively, and median PFS of 5 months and 7 months, respectively.

The value of using other recurrently mutated genes in the definition of high-risk disease and the treatment of patients with CLL is less well defined. There is data from heteroge-

FIGURE 1. Treatment Options for CLL

Optimal therapy for patients with CLL requires evaluation of disease biology, patient fitness, and treatment history. **(A)** Initial treatment of patients with CLL requires determination that they meet the International Workshop on CLL (IWCLL) criteria for active disease. These patients should then be clinically evaluated for fitness, and those considered fit for treatment then require FISH analysis for 17p13 deletion (17p-) and gene sequencing for mutations in *TP53* considered to be dysfunctional (*TP53*mut). **(B)** In patients with relapsed/refractory CLL, the response to previous treatment should also be considered when determining the treatment of choice. Patients who previously responded to chemoimmunotherapy with a response duration of 2 years or longer (late relapse) can be considered for retreatment with a chemoimmunotherapy regimen. In contrast, patients with a response duration of less than 2 years should be considered to have early relapse and should be treated with nonchemotherapy regimens.

Abbreviations: CLL, chronic lymphocytic leukemia; FISH, fluorescence in situ hybridization; Alem, alemtuzumab; BR, bendamustine/rituximab; Clb, chlorambucil; CR, complete response; FCR, fludarabine/cyclophosphamide/rituximab; Ibr, ibrutinib; Idela, idelalisib; Obi, obinutuzumab; Ofa, ofatumumab; PD, progressive disease; PR, partial response; SD, stable disease.

Modified from the Onkopedia Guidelines of the German Society of Hematology and Oncology, available at www.onkopedia-guidelines.info.

neous cohorts outside clinical trials that mutation of genes such as *NOTCH1*, *SF3B1*, and *BIRC3* could improve the prognostic accuracy of genomic analysis.[20] However, data

from the U.K. CLL4 and GCLLSG CLL8 clinical trials have only partly confirmed the independent prognostic role of these gene mutations and their effect was less pronounced

than 17p-/*TP53*mut.[19,27] An interesting finding from the GCLLSG CLL8 clinical trial was that patients with CLL and *NOTCH1* mutations had a reduced benefit from the addition of rituximab to FC.[27]

Additional biologic markers associated with inferior treatment response include unmutated *IGHV*, 11q-, increased expression of CD38, ZAP70, and CD49, and high serum levels of β2MG and TK. Nevertheless, these markers do not define a subgroup of patients with CLL who require a different standard therapeutic approach. There are ongoing efforts by an international consortium trying to integrate biologic and clinical variables into a universal risk score to predict outcome in all patients with CLL (CLL-IPI consortium, see corresponding 2015 ASCO Annual Meeting abstract). This model uses five independent predictors for OS (age, clinical stage, 17p- and/or *TP53*mut, *IGHV* status, and β2MG) in a weighted grading to define four different CLL subgroups with significantly different OS rates at 5-years (93.2%, 79.4%, 63.6%, and 23.3%; p < 0.001). This system could be an improvement on risk stratification based on staging and single parameters alone, but is limited by data from trials based on chemoimmunotherapy rather than the novel agents discussed below.

In summary, conventional chemoimmunotherapy combining an anti-CD20 antibody (rituximab, ofatumumab, or obinutuzumab) and chemotherapy (FC, bendamustine, or chlorambucil) is the standard of care in front-line CLL treatment, except for the subgroup with 17p-/*TP53*mut CLL.

Alemtuzumab-based regimens. Alemtuzumab is a humanized anti-CD52 monoclonal antibody effective against refractory CLL cells irrespective of 17p-/*TP53*mut.[31,32] However, in patients with 17p-/*TP53*mut relapsed/refractory CLL, alemtuzumab monotherapy achieves only a modest ORR of 39% to 60% and CRR of 0% to 20%, and median remission durations are short (6 to 8 months). The addition of high-dose corticosteroids to alemtuzumab for the treatment of patients with CLL with 17p- was tested in two studies. The U.K. CLL206 study administered alemtuzumab and methylprednisolone to 39 patients.[33] The German/French CLL2O study treated 131 patients with fludarabine-refractory or 17p- CLL (front-line use in 42 patients with 17p-, 28 with relapsed 17p- disease) with alemtuzumab and dexamethasone followed by ASCT or maintenance alemtuzumab.[21] Among patients with 17p- CLL who received front-line therapy, ORR from the two studies were encouraging at 88% to 97%. In the CLL206 study, the CRR was very high at 65%, but remissions were only moderately durable with a median PFS of 18 months. In contrast, remissions in the CLL2O study were more durable with a median 33 months, with the key difference being the use of postinduction therapies. The overall result (considering both front-line and patients whose disease relapsed) from CLL2O showed that ASCT was superior to maintenance alemtuzumab as postinduction therapy, with approximately 50% of transplanted patients remaining free of disease beyond 3 years. As a result of the inferior risk/benefit ratio of alemtuzumab compared with novel agents (see below) and the withdrawal of alemtuzumab from the market, these regimens have a limited role in the current management of CLL. However, the results of these studies provide a historic benchmark to compare efficacy data from phase II trials of novel agents in 17p-/*TP53*mut CLL.

The role of ASCT. There is unequivocal evidence that reduced intensity conditioning (RIC) ASCT is effective therapy in CLL, and can result in prolonged disease-free survival even for patients with advanced, chemotherapy-refractory disease.[34-39] Patients with CLL with 17p-/*TP53*mut have shown equivalent outcomes in these studies with approximately 40% to 50% of patients achieving sustained long-term remission and possibly cure, although the substantial morbidity and about 20% mortality rate restricts the use of this therapy. Factors associated with inferior outcomes included more than three prior treatment regimens, advanced clinical stage, and refractory disease at the time of RIC ASCT. Thus, RIC ASCT should be considered earlier in the course of CLL when therapeutic options for remission induction still exist, and is preferably performed in patients with low disease burden. In the chemoimmunotherapy era, consolidation with RIC ASCT would have been considered for all fit patients with CLL with early (within 24 to 36 months) relapsed or refractory disease, as well as 17p-/*TP53*mut as a component of initial treatment. The availability of more effective therapy for relapsed/refractory CLL has altered this strategy as detailed in a recent ERIC/EBMT consensus paper, which concluded that there are now few indications for RIC ASCT in the initial therapy of patients with CLL.[40] Even in early relapse and for patients with 17p-/*TP53*mut CLL, there is no universal indication for RIC ASCT and a careful consideration of the risk profile must be performed including genetics (17p-/*TP53*mut, 11q-), age, comorbidities, and degree of donor matching. To facilitate this, immediate referral of patients with early relapse and/or undergoing initial therapy for 17p-/*TP53*mut CLL to a transplant center for evaluation and counseling is recommended.

Novel Agents Targeting BCR Signaling and BCL2 in the Management of 17P/*TP53*mut CLL

The two major classes of novel agents with substantial activity across all genomic subgroups of CLL are the BCR signaling inhibitors[41-43] and the BCL2 antagonists.[44] These drugs are orally bioavailable and show dramatic efficacy and favorable tolerability compared with chemoimmunotherapy (see Relapsed/Refractory CLL below). In contrast to chemotherapy, these drugs are not genotoxic and are therefore active in patients with p53 dysregulation (i.e., 17p-/*TP53*mut). Over 200 patients with relapsed/refractory CLL with 17p-/*TP53*mut have been treated with ibrutinib monotherapy across three clinical trials[41,45,46] with excellent results compared with historic controls treated with chemoimmunotherapy. Over 80% of these patients achieved objective responses (including partial response with persistent lymphocytosis) with 12-month PFS of approximately 80% and projected 24-month PFS of approximately 50% to 60%. However, CRs were rare (< 5%), and in one study patients with 17p- CLL had a substantial increase in relapse rates com-

pared with patients without 17p- CLL.[41] In addition, the efficacy of idelalisib/rituximab appeared to not be impacted by 17p-/*TP53*mut in a retrospective subgroup analysis,[47] suggesting that this regimen is another treatment option for this subgroup.

Whereas the BCR antagonists very rarely achieve CR in the relapsed/refractory setting, the results may be different when these drugs are used as front-line therapy. For example, two CRs were recorded in the four treatment-naive patients with 17p- CLL enrolled in the ibrutinib/rituximab study,[48] and in a study of front-line idelalisib and rituximab, ORR and CRR of 100% and 33%, respectively, were reported in nine patients with 17p- CLL.[49] Prospective studies of these agents in the front-line setting are currently underway. Notably, both the U.S. Food and Drug Administration (FDA) and European Medicines Agency have granted approval of ibrutinib and the European Medicine Agency has approved idelalisib/rituximab for the up-front treatment of patients with 17p-/*TP53*mut, clearly underlining the dramatically superior efficacy of these agents in these patients. However, there are data that suggest that resistance to novel agents may be related to genomic instability of the CLL clone, resulting in either development of diffuse large B-cell lymphoma (DLBCL; Richter transformation) or acquired resistance to ibrutinib (see below).[50,51] These observations suggest that patients with 17p-/*TP53*mut CLL, which is associated with a high degree of genomic instability, could still benefit from ASCT.

The antiapoptotic members of the BCL2 family are targeted by BH3-mimetics (ABT-737, ABT-263, and ABT-199).[44,52] The current drug in clinical development for CLL is venetoclax (ABT-199, GDC-0199), which is a specific inhibitor of BCL2 and does not cause BCLXL inhibition–related thrombocytopenia.[45] The results of venetoclax in CLL have been presented in abstract form.[51,53] Both as single-agent and in combination with rituximab, venetoclax achieved high response rates of approximately 80%, and importantly—and differently from the results of BCR antagonists— complete remission rates of approximately 25% were reported even in the relapsed/refractory 17p- setting.[51,53] A number of patients have become negative for minimal residual disease (MRD) following venetoclax (with or without rituximab) therapy, and five have discontinued venetoclax in remission without recurrent disease at early follow-up. A pivotal phase II study of venetoclax in 17p- CLL (front-line and relapsed/refractory) is currently underway.

MANAGEMENT OF RELAPSED/REFRACTORY CLL
BCR Inhibitors

The importance of the BCR pathway in the pathogenesis of CLL is exemplified by the use of stereotypic immunoglobulin variable regions, biased *VH* gene family usage, prognostic implications of mutational status, and the profound clinical efficacy of the BCR pathway inhibitors in CLL (reviewed in Jones[43] and Stevenson[54]). As a result of their novel mechanisms of action, BCR antagonists have required a re-evaluation of several key aspects of our management practices in CLL. First,

the initial lymphocytosis seen with these agents would be considered progressive disease based on the standard IWCLL criteria.[1] This lymphocytosis likely results from the inhibition of several adhesion molecule pathways, including CXCR4/5, and could contribute to the efficacy of these agents.[55,56] Fortunately, the lymphocytosis is usually accompanied by a very rapid decrease in lymphadenopathy, and improvement in cytopenias and symptoms. As a result, the IWCLL criteria have been revised by a group sponsored by the Lymphoma Research Foundation[57] to exclude use of lymphocytosis as the sole indicator of progression in patients who are receiving treatment with a BCR antagonist. This new response category has been termed "PR with lymphocytosis."

Second, maximal response is often measured shortly after the completion of therapy. The German CLL Study Group validated the prognostic effect of measuring MRD 2 months after completion of cycle six in the CLL8 study.[18,58] For the BCR signaling pathway inhibitors, responses evolved over time[41] and treatment is often ongoing. Patients receiving treatment typically move from stable disease (or partial response with lymphocytosis) to partial response when the lymphocytosis resolves, to CR. Although we know the median time to response to treatment, the median time to CR has not yet been determined because half of the population has not yet achieved CR or had progressive disease. In addition, although we can assume that negative MRD studies will predict for an excellent outcome, the presence of MRD can no longer be seen as indicative of a poor response. Thus, comparison of responses to therapy with BCR signaling inhibitors to chemoimmunotherapy in clinical trials should not use the previously used conventional endpoints of partial response, CR, and MRD status, but should rather focus on PFS and OS.

The third issue to re-evaluate is the role of prognostic markers. Although the prognostic markers commonly used in clinical practice (CD38, ZAP70, *IGHV* mutation status, and interphase FISH) retain their predictive value for time to treatment, they do not predict response to treatment with BCR antagonists.[41,42] It is also worth noting that in the first publication of the phase II data on ibrutinib therapy in CLL,[41] patients with mutated *IGHV* were reported to have poorer responses. However, analysis at a later time point showed no difference in response rates based on *IGHV* mutation status.[59] The initial difference could have been because the CLL cells in patients with unmutated *IGHV* were more dependent on BCR signaling, and therefore more sensitive to its inhibition. With regard to possible predictors of resistance developing to ibrutinib, complex karyotype and a "mutator phenotype" might predict for the development of resistance. Resistance to ibrutinib has been shown to occur because of a single base pair mutation resulting in a cysteine-to-serine change at amino acid 481 in BTK that alters the ibrutinib binding site, or gain-of-function mutations in the *PLCγ2* gene that overcome the inhibition of BTK.[50,60] These data alter the role of use of prognostic factors in treatment planning for patients with CLL. Important considerations include the role of ASCT and the ability to avoid DNA-damaging drugs that

could be associated with the increased risk of secondary myeloid neoplasms[61] and other second malignancies (see below).

Ibrutinib therapy. Ibrutinib was the first BCR pathway inhibitor approved for treatment in CLL. The phase I study demonstrated a wide therapeutic window, with all patients who were treated with doses of ibrutinib greater than 2.5 mg/kg demonstrating complete inhibition of BTK at 4 hours. Two subsequent phase II studies used a fixed dose of ibrutinib of 420 mg/day. Patients with relapsed/refractory CLL study who received ibrutinib experienced a 90% ORR. Response were durable and the median PFS had not been reached at a median follow-up of 35.2 months, with an estimated PFS of 69% at 30 months.[41,59] In the study of initial therapy of previously untreated CLL patients with progressive disease over the age of 65, the ORR including partial response with lymphocytosis was 84%, with an estimated PFS of 96% at 30 months. Of the 31 patients enrolled in this study, three discontinued treatment for adverse events, two patients withdrew consent, and one patient demonstrated progressive disease in the form of a Richter transformation that was diagnosed at month 8.

Overall, treatment with ibrutinib was well tolerated, with the most common adverse events reported being transient diarrhea (58%), fatigue (28%), infections (32%), and bleeding (61%). The diarrhea appeared to be transient with a median duration of 20 days and was only severe ($\geq$ grade 3) in 6% of patients. Diarrhea was controllable in most patients with antimotility agents and only led to treatment discontinuation in one patient, and ibrutinib dose reductions in two patients. The frequency of severe infections was considerably higher in patients with relapsed/refractory disease compared with previously untreated patients (51% vs. 13%). In addition, the frequency of severe infections was highest in the first year of treatment and then decreased in subsequent years for both relapsed/refractory (36%, 32%, and 24%) and previously untreated (10%, 8%, and 4%) disease. Long-term ibrutinib therapy did not appear to increase the risk of infection in these patients.[41,59,62] Bleeding was reported in 61% of CLL patients treated with ibrutinib and was severe in 8% with one death. Bleeding resulted in treatment discontinuation in three patients. In these studies, 58% of patients were receiving antiplatelet agents and 22% were receiving anticoagulants.[41,59,62]

An obvious shortcoming in when evaluating phase II data is the lack of a control population to assess what would be the expected adverse events in the population being studied. When ibrutinib was compared to ofatumumab in the RESONATE study, several important findings related to adverse events were noted. First, fatigue was seen in equal numbers in both arms (28% ibrutinib vs. 30% ofatumumab). Second, severe infections were seen in similar numbers in both arms (24% ibrutinib vs. 22% ofatumumab). Third, atrial fibrillation, an adverse event not previously attributed to ibrutinib in phase II trials, was found to occur more frequently in patients treated with ibrutinib compared with ofatumumab (4% ibrutinib vs. 1% ofatumumab). Whether atrial fibrillation is associated with ibrutinib treatment will require

subsequent phase III trials to ascertain, but for now, clinicians might consider cardiac risks when making treatment decisions.

Data for ibrutinib in patients with 17p- CLL are derived from three studies.[46,49,63,64] In the pivotal RESONATE study, 127 of the 391 patients had 17p-. The overall response rate, excluding partial response with lymphocytosis, was 47.6% with ibrutinib, compared with 4.7% with ofatumumab. The median PFS for ibrutinib was not reached compared with 5.8 months for ofatumumab. In patients who received ibrutinib, 83% with 17p- were progression-free at 6 months. There was no difference in response rate or PFS based on the presence or absence of 17p-.[46] An NIH phase II study of 51 patients with *TP53* aberrations demonstrated a 97% response rate in previously untreated patients, with a 91% PFS at 24 months (35 patients), and an 80% response rate in previously treated patients, with an 80% PFS at 24 months (16 patients). The third study, RESONATE-17, involved 144 patients with CLL with 17p- whose disease had relapsed or was refractory to one prior therapy. The overall response rate was 82.6%, with a PFS at 12 months of 79.3%. Progressive disease occurred in 20 patients (13.9%), including Richter transformation in 11 patients, seven of which occurred within the first 24 weeks of treatment.[49,64] These data suggest that treatment of patients with relapsed/refractory CLL and 17p-/*TP53*mut using ibrutinib results in better outcomes than that achieved with any previously used therapies.

Idelalisib therapy. Idelalisib, which targets PI3K-delta, demonstrated excellent efficacy and tolerability in patients with relapsed/refractory CLL. Across its phase I/II studies, idelalisib used as a single agent resulted in a 72% response rate with a median PFS of 15.8 months[65] in a high- to very high-risk relapsed/refractory CLL population (70% treatment-refractory, 24% 17p-/*TP53*mut). Severe adverse events included diarrhea/colitis (5.6%), transaminitis (1.9%), and pneumonia (20.4%).

Idelalisib's pivotal phase III study was conducted in a heavily pretreated population of patients considered unlikely to benefit from chemotherapy because of a previous response duration of less than 2 years who had additional comorbidities (persistent myelosuppression or creatinine clearance < 60 mL/min).[42] Two-hundred and twenty patients were randomly assigned to receive rituximab/placebo or rituximab/idelalisib (150 mg twice daily). The patient population had a median CIRS score of eight, median creatinine clearance of 64.5 mL/min, and 43.5% had 17p-. The study met its primary endpoint at the first interim analysis with an 85% reduction in the risk of progression or death between the two arms (median PFS, 5.5 months for placebo vs. not reached for idelalisib) and a substantial improvement in OS (survival at 12 months of 80% for placebo vs. 92% for idelalisib). A subsequent update after the second interim analysis demonstrated a 12-month PFS for the idelalisib/rituximab arm of 66% compared with 13% for the placebo/rituximab arm.[47] PFS and response rates were not affected by prognostic factors, including deletion 17p-/*TP53*mut, ZAP70 expression, or *IGHV* mutational status. Severe adverse events occurred in

40% compared with 35% of patients for idelalisib or placebo, respectively. Severe adverse events of note for idelalisib compared with placebo included diarrhea (19% vs. 14%), pneumonia (6% vs 8%), and transaminitis (35% vs. 19%). The risk of rituximab infusion reactions decreased with idelalisib compared with placebo (15% vs. 28%).

BCR inhibitor therapy. The studies detailed above have clearly demonstrated the effectiveness of ibrutinib and idelalisib as treatments for CLL patients. The FDA approvals for these agents reflects the populations studied in the clinical trials; ibrutinib has been approved for the initial therapy of CLL in patients with 17p- and for all patients with relapsed/refractory disease, and idelalisib has been approved for use in combination with rituximab for patients who are considered candidates for treatment with single-agent rituximab. Choice of the best BCR antagonists for an individual patient should currently be based on the toxicity profiles of ibrutinib and idelalisib. For ibrutinib, the risks of bleeding, diarrhea, atrial fibrillation, and drug interactions affecting CYP3A4 are the most worrisome. Idelalisib can cause liver injury, inflammatory colitis, and pneumonitis, and should be avoided in patients with hepatic dysfunction or autoimmune diseases.

The optimal duration of therapy with BCR has not yet been determined. Because these therapies are effective and relatively well tolerated, it could be reasonable to continue treatment. However, we do not yet know the long-term effects of continuing therapy and conversely have little data on the mechanisms of resistance and how development of resistance may be affected by stopping treatment. Studies are currently underway looking at discontinuing therapy once patients reach MRD negativity. Until the data from these studies are available, it is prudent to continue patients on therapy indefinitely.

COMPLICATIONS OF CLL

Acquired immune defects occur early in the course of CLL and increase the risk of infection and autoimmune disease. Defective immune surveillance could also contribute to the increased risk of second malignancy. In addition, clonal evolution can cause transformation to DLBCL.

Infections

Patients with CLL have a high risk of serious infection, which causes considerable morbidity and mortality.[66] Defective nonmalignant B-cell function impairs humoral responses to antigens, and although absolute T-cell counts are usually increased, CD4/CD8 ratios are reversed with decreased T-cell receptor repertoire, and impaired T-cell function.[66-68] Monocyte, dendritic, and natural killer cell dysfunction, decreased serum complement levels, and bone marrow failure–associated neutropenia result in defective innate immunity.[66,69-71] Immune dysfunction is further impaired by chemotherapy and monoclonal antibody therapy.

Clinical. Impaired humoral immunity increases the risk of bacterial infections by encapsulated organisms (e.g., *Streptococcus pneumoniae* and *Staphylococcus aureus*) in all stages of CLL.[66,68,72] T-cell defects increase the risk of herpesvirus reactivations. The clinical consequences include shingles (frequently complicated by postherpetic neuralgia), disseminated varicella zoster, herpes simplex infections (including lymphadenitis), and cytomegalovirus-induced disease.[66,73-75] The risk of herpesvirus reactivation is increased by treatment with lymphotoxic drugs (e.g., purine analogs, corticosteroids, and alemtuzumab) that can cause prolonged T-cell lymphopenia. Patients with advanced-stage CLL and those undergoing immunosuppressive therapy or ASCT are at high risk of contracting fungal and atypical bacterial infections. Major concerns are *Pneumocystis jiroveci* pneumonia, cryptococcal meningitis, and systemic histoplasma, *Aspergillus*, *Nocardia*, *Candida*, and atypical Mycobacteria infections.[66]

Prevention. Active monitoring and treatment of patients with CLL can decrease the risk of serious infections and their complications. Patient education is essential and should emphasize the need for immediate medical evaluation of systemic infections and fevers at 38.5°C or higher. Vaccination efficacy is suboptimal in patients with CLL.[66,76,77] Pneumococcal vaccine responses are improved by the use of the conjugated 13-valent vaccine, and additional use of the 23-valent polysaccharide pneumococcal vaccine, as well as the influenza vaccine, could be of value, especially in patients with early-stage CLL.[76,77] Live vaccines (e.g., shingles and yellow fever) are contraindicated.[66,73]

There are limited data on the efficacy of the use of prophylactic antimicrobial therapy in CLL.[66] *Pneumocystis* and herpesvirus prophylaxis is commonly used during and for 3 to 6 months after treatment with purine analog–containing chemoimmunotherapy, alemtuzumab, and high-dose corticosteroids.[73] Prophylactic antiviral therapy can decrease the risk of recurrent varicella zoster and herpes simplex infection in patients with recurrent infections.[73]

Intravenous immunoglobulin (IVIG) can normalize serum IgG levels and decrease the risk of infections but has not been shown to improve survival.[66,78] IVIG therapy can cause serious toxicities and is time consuming and expensive. Use should probably be limited to patients with recurrent major infections (two or more in 6 months).

Effective management of established infections in patients with CLL requires a vigorous effort to determine the cause of infection with a high index of suspicion for encapsulated bacteria, atypical, and opportunistic infections. Therapy planning should assume that all CLL patients are immunocompromised.

Hematologic Autoimmune Disease

Patients with CLL have an approximate 5% to 10% lifetime risk of hematologic autoimmune complications,[79-81] but CLL related nonhematologic autoimmune complications are rare.[82]

In most (> 90%) patients with CLL and autoimmune cytopenia, loss of immune self-tolerance results in the produc-

tion by nonmalignant B cells of pathologic high affinity polyclonal IgG antibodies directed against blood cell antigens.[81] Self-reactive monoclonal antibody production by CLL cells (usually IgM) causes less than 10% of autoimmune hemolytic anemia (AIHA) in patients with CLL.[81] Pure red blood cell aplasia (PRCA) can be mediated by either pathologic autoantibodies or T-cell dysfunction. Autoimmune cytopenias can occur at any time in the course of CLL and are the cause of approximately 15% to 20% of noniatrogenic cytopenias in patients with CLL.[79-81] Onset can be acute or insidious. Patients with CLL should not be classified as advanced-stage disease because of their autoimmune cytopenia.[1,79-81]

AIHA: clinical. AIHA is the most common autoimmune complication of CLL and is characterized by reticulocytosis in the absence of bleeding, elevated lactate dehydrogenase and indirect bilirubin, and a positive direct antiglobulin test (DAT).[79] DAT tests detecting red blood cell (RBC)–bound anti-RBC IgG antibodies and the complement degradation product C3 are positive in over 90% of patients with CLL and AIHA. However, approximately 15% to 20% of all patients with CLL have a positive DAT during the course of their disease and only about 35% of these patients develop AIHA. The diagnosis of AIHA thus requires definitive evidence of hemolysis.[83,84] Patients with CLL with both AIHA and CLL-related bone marrow failure (complex AIHA) often do not have a reticulocytosis. These patients require a diagnostic bone marrow biopsy to ensure an accurate diagnosis of the cause of their cytopenia and thus appropriate treatment.

AIHA: management. Patients with AIHA and adequate erythropoiesis (simple AIHA) usually respond to immunosuppression with corticosteroids.[81] More rapid responses can be obtained with IVIG.[81] However, responses are not usually sustained when immunosuppression is decreased and patients frequently require long-term immunosuppression or additional treatment such as anti-CD20 monoclonal antibodies.[81] Patients with both AIHA- and CLL-related bone marrow failure require therapy that treats both their CLL and autoimmune complication. Purine analogs should be used with caution because myelosuppression can exacerbate the anemia and the risk that monotherapy can precipitate autoimmune complications of CLL. Combination therapies including alkylating agents (cyclophosphamide or bendamustine), corticosteroids, and anti-CD20 monoclonal antibodies are usually effective.[85,86] There is preliminary data that therapy with B cell receptor pathway inhibitors could be effective. Splenectomy is of limited value.

ITP: clinical. Patients with CLL with cytopenia caused by progressive bone marrow failure usually develop anemia followed by thrombocytopenia.[2] Patients with CLL who have thrombocytopenia without anemia should be evaluated for etiologies other than bone marrow failure including increased platelet sequestration. Those with insidious onset thrombocytopenia and platelet counts greater than 50×10^9/L should be evaluated for hypersplenism. Acute onset (<

2 weeks) or more severe thrombocytopenia (platelet counts $< 50 \times 10^9$/L) in patients with CLL is more likely to be caused by ITP, which still remains a diagnosis of exclusion. Antiplatelet antibodies have low specificity and sensitivity and are of limited diagnostic value.[81] The diagnosis of ITP thus requires a bone marrow biopsy to exclude other potential etiologies and demonstrate adequate megakaryocytopoiesis.

ITP: management. Patients with stable ITP without bleeding complications and platelet counts above approximately 20 to 30×10^9/L should be carefully observed and educated, but do not require treatment.[81] Patients with CLL and ITP without evidence of bone marrow failure should be treated with immunosuppression with the addition of thrombopoietin agonists if required. Splenectomy is less effective compared with primary ITP.[81] Patients with both ITP and bone marrow failure can be treated with the same regimens used to manage complex AIHA except that BTK inhibitors (e.g., ibrutinib) that affect platelet function and increase the risk of bleeding should be avoided.

PRCA: clinical. PRCA usually presents as progressive anemia with a very low absolute reticulocyte count and no evidence of hemolysis.[81] Definitive diagnosis requires a bone marrow study. The differential diagnosis includes parvovirus and other viral infections. Clinical testing for pathologic antibodies or T cells is not routinely available.

PRCA: management. PRCA responds slowly to immunosuppression (e.g., prednisone and cyclosporine) because of the lag time to restoration of erythropoiesis. Long-term immunosuppression (e.g., low dose cyclosporine) is frequently required to maintain adequate hematopoietic levels.[81,87]

Autoimmune neutropenia. This is a rare and poorly understood condition which should be considered in the differential diagnosis of patients with isolated neutropenia of uncertain etiology.[81,87]

Nonhematologic Autoimmune Disease

Patients with CLL have an increased risk of autoimmune acquired angioedema, paraneoplastic pemphigus, and glomerulonephritis.[74,82] A clinically important consequence of immune dysregulation in CLL is exaggerated cutaneous arthropod bite reactions.[74] These can be complicated by cellulitis and systemic infections.

Hematologic Second Malignancies

Lymphoid malignancies. Patients with CLL have an increased risk of second lymphoid malignancies.[88] The highest risk is for DLBCL (approximately 0.5% per year). DLBCL can occur at any time in the course of CLL and is more frequent in patients with *NOTCH1* mutations and 17p-/*TP53*mut.[89,90] The most common etiology of DLBCL (about 80%) is clonal transformation of a CLL cell and these patients have a poor

prognosis.[91] In contrast, approximately 20% of patients with CLL have clonally-unrelated DLBCL, which has a considerably better prognosis.[91] This clinically important distinction between clonally-related and -unrelated DLBCL can be made by *VDJ* rearrangement analysis of CLL and DLBCL cells.[91] Patients with CLL are also at an increased risk of developing Hodgkin lymphoma and other B-cell malignancies.

There is no standard of care for second lymphomas in patients with CLL. Patients with nonclonal DLBCL should be treated as having de novo disease.

Nonhematologic Second Malignancies

Skin cancer. Patients with CLL have a markedly increased risk of skin malignancies. Squamous cell carcinoma and basal cell carcinoma rates are increased by approximately 5- to 10-fold and these malignancies are more likely to be locally aggressive and metastatic.[74,92-94] Melanoma is also more common and aggressive with poorer outcome.[88,92,93,95]

Patients require education on avoidance of ultraviolet radiation and should be evaluated by a dermatologist at diagnosis and then at least annually. Patients and families need to be educated on how to conduct monthly skin inspections.

Other malignancies. Noncutaneous second malignancies are a major cause of morbidity and mortality in patients with CLL.[88,92,96,97] Patients should be encouraged to avoid smoking and excessive alcohol use, and to undergo routine preventative screening.

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MELANOMA/SKIN CANCERS

Cutaneous Squamous, Basal, and Merkel Cell Cancers

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Prognostic Factors and the Role of Adjuvant Radiation Therapy in Non-Melanoma Skin Cancer of the Head and Neck

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OVERVIEW

Non-melanoma skin cancer (NMSC) is the most common cancer worldwide. Among the two types of NMSC, basal cell carcinoma (BCC) accounts for approximately 75% to 80% of cases and cutaneous squamous cell carcinoma (cSCC) accounts for 20% to 25% of cases. The majority of lesions are low risk and treated with simple surgical excision, which provides histopathologic information and is associated with high cure rates and acceptable cosmetic and functional outcomes. cSCCs are generally more aggressive than BCCs. NMSC commonly occurs in the sun-exposed head and neck region (80% to 90%). Approximately 5% of patients with NMSC (mainly cSCC) will have clinicopathologic features that predict for an increased risk for local and regional recurrence and, rarely, distant relapse. These features include locally advanced primary disease (stage T3-T4), regional nodal involvement, clinical perineural invasion, recurrent disease following treatment, and immunosuppression. Patients who have these features may warrant review by a multidisciplinary tumor board and might require combined modality treatment involving surgery and adjuvant radiation therapy (RT). This article focuses on our current understanding of the prognostic factors and role of adjuvant RT in high-risk NMSC of the head and neck.

Non-melanoma skin cancer is the most common cancer worldwide and represents a major global economic and health burden. Approximately 2.5 to 3.5 million individuals in the United States are diagnosed with an NMSC each year, with approximately 75% to 80% of diagnoses consisting of BCC and 20% to 25% consisting of cSCC.[1,2] The sun-exposed head and neck is the most common region affected (80%) with incidence rates continuing to rise.[2] Australia, which has the highest skin cancer rates in the world, has an age-standardized incidence rate of 387 cases per 100,000 individuals for cSCC and 884 cases per 100,000 individuals for BCC.[3] cSCC tends to be more aggressive than BCC.

The majority of patients with NMSC (95%) are at low risk for relapse and are typically treated with simple excision or, less commonly, with RT where surgery is not preferred. However, up to 5% of patients (mainly with cSCC) may harbor clinicopathologic high-risk features predicting for an increased risk for local and regional (locoregional) recurrence, or, rarely, distant relapse and death.[2] Factors that predict for high-risk disease include locally advanced disease (American Joint Committee on Cancer [AJCC] and Union for International Cancer Control [UICC] stages T3-T4), regional nodal involvement, clinical perineural invasion (cPNI), recurrent disease following treatment, and immunosuppression. Patients who have disease with these characteristics often warrant review by a multidisciplinary tumor board and treat-

ment with combined-modality therapy consisting of surgery and adjuvant RT.

This article will primarily focus on our current understanding of the prognostic factors in NMSC, the management of high-risk disease, and the role of adjuvant RT. The article will not discuss low-risk disease, the role of definitive or palliative RT, or the role of other treatment modalities beyond adjuvant RT.

PROGNOSTIC FACTORS
Clinicopathologic Factors
Studies have identified a number of adverse clinicopathologic prognostic factors that predict for recurrence in NMSC. The majority of recurrences tend to occur within 2 years of the initial primary diagnosis.[4] BCC and cSCC generally share the same risk factors for locoregional recurrence, although regional recurrences in BCC seldom occur. Many of the factors that predict for local recurrence in both BCC and cSCC also tend to predict for regional nodal involvement or relapse. In BCC, the development of distant metastases is rare ($\leq$ 1%).[4,5,6] Division into low- and high-risk categories for NMSC is somewhat arbitrary since the disease falls on a continuous spectrum, as determined from retrospective series reports that found different prognostic factors between published series.

A review by Alam and Ratner reported that the risk for local recurrence and metastases for cSCC increases in the presence of factors such as rapid growth, greater than 2 cm diameter, primary site of lip or ear, immunosuppression, previous RT, recurrence, greater than 4 mm thickness or Clark level IV, poor differentiation, infiltrative or peripheral margins, spindle or acantholytic features, and perineural invasion (PNI).[2]

Brantsch et al published the results of a prospective study assessing the risk factors for recurrence and regional metastases in cSCC. They reported that patients with a tumor thickness of 2.0 mm or smaller did not develop metastases. Metastases occurred at a rate of 4% among patients with tumors between 2.1 to 6.0 mm and 16% for tumors larger than 6.0 mm. The risk for local recurrence depended on increasing tumor thickness and desmoplasia.[5]

The National Comprehensive Cancer Network (NCCN) has produced a table detailing high- and low-risk factors for recurrence of BCC and cSCC based on a combination of available evidence and workshop group consensus.[6]

Clayman et al identified several factors that reduce disease-specific survival (DSS) in patients with cSCC. These factors include local recurrence at presentation, increasing tumor size and depth, invasion beyond subcutaneous tissues, and PNI. Patients with one or more risk factors, when compared with patients with no risk factors, had a significantly inferior 3-year DSS of 70% vs. 100%, respectively (p < 0.001, log-rank test).[7]

PNI, immunosuppression, and regional nodal involvement are well-recognized prognostic risk factors for LRC and distant relapse, and are discussed in greater detail below.

Table 1 summarizes the commonly accepted prognostic risk factors in NMSC of the head and neck.

KEY POINTS

- Non-melanoma skin cancer (NMSC) is the most common cancer worldwide. Approximately 75% to 80% of cases are basal cell carcinoma and 20% to 25% of cases are cutaneous squamous cell carcinoma.
- Division into low- and high-risk NMSC is somewhat arbitrary since disease type falls on a continuous spectrum, as data from retrospective series have shown.
- Approximately 5% of patients with NMSC (mainly cutaneous squamous cell carcinoma) are considered to be at high risk for relapse, either local, regional, or distant (rarely), following surgery.
- Because of the dearth of high-level evidence on the benefits of adjuvant radiation therapy (RT), there is a lack of universally adopted guidelines regarding its use. Use of adjuvant RT is commonly based on individual institutional policy.
- Retrospective series support consideration of adjuvant RT in the presence of advanced primary disease (stages T3-T4), regional nodal involvement, clinical perineural invasion (cPNI) and immunosuppression.

TABLE 1. Prognostic Risk Factors for Relapse of NMSC of the Head and Neck

Risk Factors	Low Risk	High Risk
Tumor size and T-stage (AJCC/UICC)	≤ 2 cm	> 2 cm
	T1-2	Stages T3-T4
Tumor thickness (SCC)	< 2 mm	≥ 2 mm
		Clark level ≥ 4
Sites		Lip, mask areas of face
Differentiation	Well	Poor
Subtype (SCC)		Basosquamous, desmoplastic, adenosquamous
Perineural invasion	Absent or single small nerve	Multifocal small nerve, named nerve
Rapid growth	Absent	Present
Borders	Well-defined	Poorly defined, in-transit
Lymphovascular space invasion	Absent	Present
Margin status	Negative	Positive
Immune status		Immunosuppressed
Chronic inflammation, scars (SCC)	Absent	Present
Previous radiation therapy	Absent	Present
Nevoid basal cell carcinoma syndrome* (BCC)	Present	Absent
Recurrent disease	No	Yes

Abbreviations: NMSC, non-melanoma skin cancer; AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control; SCC, squamous cell carcinoma; BCC, basal cell carcinoma.
*Also known as Gorlin syndrome.

Perineural Invasion

PNI can be divided into two categories: (1) disease detected incidentally on pathologic assessment (pPNI) and (2) involving a named nerve (cPNI). For patients with cPNI, a prior history of pPNI is not always present.

PNI is more frequently seen in patients with cSCC (5% to 10%) than in patients with BCC (2% to 5%).[8,9] In the case of cPNI, the Trigeminal (V) and Facial (VII) cranial nerves (CN) are commonly affected, typically involving retrograde progression (progression of disease from the periphery (skin) toward the brain/brainstem). Diagnosis may be delayed with VII CN involvement because of an initial misdiagnosis of Bell's palsy. Diagnosis can be facilitated with the use of targeted 3 Tesla MRI neurography, which provides superior sensitivity and specificity compared with computed tomography (CT).[10]

There is some evidence that extratumoral disease (PNI seen extending beyond the main tumor mass), large nerve diameter involvement, and multifocal PNI are associated with more aggressive disease behavior.[8,11]

cPNI is more aggressive when seen in cSCC compared with BCC. Jackson et al reported 5-year local control (LC) rates of 90% for pPNI compared with 57% for cPNI (p < 0.0001). The pPNI and cPNI groups also differed in relapse-free survival (76% vs. 46%, p = 0.003), DSS (90% vs. 76%, p = 0.002), and

overall survival (OS) (69% vs. 57%, p = 0.03). In a study of 55 patients, patients with pPNI with BCC histology had better LC rates compared with patients with pPNI with SCC histology (97% vs. 84%, p = 0.02).[12]

In a recent study of 114 patients with PNI, patients whose tumors met two criteria—greater than 2 cm and associated with other multiple unfavorable features (including lymphovascular invasion and deep invasion)—were at increased risk for death.[8] The authors suggested that patients with PNI of small caliber nerves (< 0.1 mm) and no other unfavorable risk factors are likely to have a better outcome. Further studies are required to better establish the interaction between PNI and other non-PNI prognostic risk factors.

IMMUNOSUPPRESSION

The importance of immunosuppression as a factor that increases the risk for both developing NMSC and experiencing poorer outcomes is well documented.[2,4] Patients with immunosuppression are more likely to develop regional nodal metastases, to be at greater risk for death, and to have tumors that exhibit higher rates of adverse risk features such as PNI.[2,13] In a study by Tomaszewski et al, 36% of patients with node-negative cSCC and chronic lymphocytic leukemia developed regional nodal recurrence, with disease-specific death reported for 33% of patients.[14]

REGIONAL NODAL METASTASES

The presence of primary disease with high-risk features, predominantly cSCC, increases the risk for regional nodal metastatic disease; the most common sites of regional involvement are intraparotid nodes, followed by cervical nodes.[15,16] The presence of regional nodal metastases is an adverse feature and predicts for inferior DSS and OS.[15,16,17,18] Depending on the extent of node disease, reported regional relapse rates following therapeutic surgery alone range between 20% and 80%.[16]

Although there is no universal consensus or high-level evidence to support the role of adjuvant RT following nodal surgery, research has identified a number of nodal metastatic prognostic factors that warrant consideration for combined modality treatment (these prognostic factors were identified mainly through retrospective series).[16] Table 2 presents a summary of these metastatic nodal prognostic factors. A study by Veness et al that examined the outcomes of patients with metastatic cSCC found that increasing nodal size (≥ 3 cm), multiple node involvement (≥ 2), and extranodal spread were associated with worse survival.[19] Another study, which reported on the outcomes of 250 patients with metastatic cSCC following treatment, found that the majority of recurrences (50 out of 70 patients; 73%) were regional and that several factors—immunosuppression, the presence of extranodal spread, and positive margins—were associated with inferior survival.[13]

Ebrahimi observed an excellent outcome in a subset of patients with one involved node, smaller than 3 cm in maximal

TABLE 2. Summary of Metastatic Nodal Prognostic Factors (High-Risk Nodal Disease) that Predict for Relapse after Treatment and Disease-Specific Survival

Prognostic Factor
> 3-cm node
≥ 2 nodes
Extracapsular extension
Positive/close margins (≤ 5 mm)
Dermal or in-transit metastases
Invasion into surrounding structures (e.g., bone, cranial nerves)
Recurrent disease after initial surgery
Immunosuppression

diameter, and no ECE. Three-year DSS in this patient subset was 97% following intraparotid and/or cervical node surgery alone.[20]

In addition, surgical series have shown that in the presence of intraparotid node disease, the risk for synchronous occult cervical node disease ranges between 15% and 45%, with range results between 15% and 20% reported in contemporary series that use modern imaging techniques; the data from the series justifies considering elective cervical nodal treatment for this group.[21]

TREATMENT

A number of guidelines recommend that complex and high-risk cases should be referred for consultation and management by a multidisciplinary tumor board. These cases may require the primary disease to undergo extensive resection with reconstructive surgery, elective or therapeutic nodal treatment, adjuvant RT, and close follow-up monitoring.[4,6] Table 3 summarizes the factors that might be considered for a referral to a multidisciplinary tumor board.

TABLE 3. Considerations for Referral to Multidisciplinary Tumor Board

Locally advanced primary disease (UICC/AJCC stages T3-T4) or in-transit disease
Difficulty obtaining complete margins
Clinical perineural nerve invasion
Cosmetic considerations
Immunosuppression
Suspected/confirmed lymph node metastases
Tumors in complex locations (lip, eyes)
Multiple primary lesions (e.g., nevoid basal cell carcinoma syndrome)
Distant metastases

Abbreviations: AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control.

ADJUVANT RADIATION THERAPY

High-level randomized evidence confirming the benefit of adjuvant RT in advanced NMSC is lacking. NCCN clinical practice guidelines in oncology for NMSC acknowledge this fact, stating that its recommendations are based on low-level evidence (the evidence is in the 2A category, meaning there is uniform NCCN consensus that the intervention is appropriate).[6]

The use of adjuvant RT is based on data from retrospective studies (which are acknowledged to be inherently biased) that have shown that adjuvant RT reduces rates of recurrence when used in advanced disease, such as regional nodal metastatic cSCC.[13,15-18] There is a lack of universal guidelines that describe which adverse prognostic factors warrant adjuvant RT therapy and, therefore, the use of this therapy is typically based on institutional policy. The Trans Tasman Radiation Oncology Group has completed accrual to a randomized trial (TROG 05.01 NCT00193895) comparing the role of adjuvant concurrent chemoradiotherapy with the role of adjuvant RT in high-risk cSCC. High-risk disease was defined as and stratified into locally advanced primary disease (AJCC or UICC stage T3-T4 or in-transit disease) and high-risk nodal disease (defined as any of the following: extracapsular extension of any node size, intraparotid nodal metastasis regardless of size or number, two or more cervical nodes, and/or cervical node(s) that are 3 cm or larger). RT consisted of 60 Gy over 6 weeks, with 2 Gy fractions daily, with or without weekly carboplatin (AUC 2).

Table 4 summarizes indications where adjuvant RT may be considered. However, Table 4 does not include a number of other clinicopathologic prognostic factors for relapse, including lymphovascular invasion, rapid growth, and pPNI. These factors have been left out because there remains a question about the benefit of adjuvant RT in the presence of these factors and about the extent of disease where the benefit is seen.

ADJUVANT REGIONAL NODAL TREATMENT

Intraparotid and cervical nodes are the most common regional nodal basins involved in cSCC of the head and neck. Veness et al found that among patients whose cSCC had metastasized to lymph nodes, those who were receiving surgery/RT had a statistically superior 5-year disease free survival compared to patients receiving surgery alone (73% vs. 54%, respectively; p = 0.004).[18]

Unlike in mucosal head and neck SCC, the role of adjuvant chemoradiotherapy in high-risk disease is unknown. However, based on the NCCN guidelines and publications from Cooper et al and Bernier et al, some institutions have adopted the use of adjuvant chemoradiotherapy for high-risk disease, particularly in the presence of regional nodal metastatic SCC with extracapsular extension.[6,22,23] The TROG 05.01 (NCT00193895) is the only randomized trial currently examining the role of adjuvant chemoradiotherapy in high-risk cSCC, with results expected mid-2016.

ELECTIVE NODAL TREATMENT

Elective nodal treatment is often considered when the perceived risk for occult nodal involvement is around 15% to 20%. The risk for occult nodal involvement is based on the presence of high-risk clinicopathologic prognostic factors. In cases where regional nodal involvement is suspected, CT is typically used to stage the neck. However, the sensitivity and specificity of CT for nodal involvement is reduced when nodal diameter is smaller than 1 cm. Positron emission tomography (PET) appears to have a higher sensitivity and specificity than CT in the nodal staging of mucosal head and neck cancer.[24] It is likely that PET has a similar utility in cSCC, but this is yet to be confirmed in clinical studies.

Elective nodal treatment may consist of either elective nodal dissection, or, in cases where adjuvant RT is recommended for the primary site, the nodal basin may be treated electively with RT at the same time.

Although there is some evidence showing that sentinel lymph node biopsy may improve the detection of occult node disease, its routine use is not currently universally practiced.[25]

ADJUVANT PERINEURAL INVASION TREATMENT

The challenge in managing patients with cPNI is in achieving durable control. Despite the absence of randomized controlled studies, en bloc resection and adjuvant RT may offer select patients the best chance of cure. Tumors previously considered unresectable, such as those with intracranial PNI up to the gasserian ganglion (zone 2), may be operable and have the potential to improve patient survival.[26] However, this type of major surgery can require craniotomy, and thus is best limited to appropriately selected patients in specialized units. Furthermore, it is uncertain whether this type of surgery has substantially greater benefit compared with highly conformal intensity-modulated RT alone.[27,28] The role of elective nodal treatment and/or postoperative concurrent chemotherapy and RT in cPNI in the absence of other adverse risk factors remains inconclusive.

Gluck et al analyzed patterns of failure and proposed to include the following in the target volume: the portions of the

TABLE 4. Clinicopathologic Factors Indicating Consideration of Adjuvant Radiation Therapy*

UICC/AJCC stages T3-T4 or in-transit disease
Clinical perineural invasion
Recurrent primary disease
High-risk nodal disease
Immunosuppression

Abbreviations: AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control.
*Postoperative radiation therapy is considered for sites where margins are incomplete or close (≤ 5 mm) and further surgery is not feasible or preferred.

nerve that are proximal and distal to the tumor site, skin that is innervated by the involved nerve, major communicating branches, and the compartment in which the nerve is embedded, such as the parotid gland for CN VII.[29]

ADJUVANT RADIATION THERAPY VOLUMES AND DOSES

The preferred minimum clinical target volume (CTV) margin on the resected primary tumor is 1.0 cm, although this may not always be possible depending on its proximity to organs at risk. For resected node disease, the preferred minimum CTV margin is 0.5 to 1.0 cm.

The doses used in adjuvant RT are similar to those used in mucosal head and neck cancer, and are not based on prospective data specific to NMSC. The NCCN guidelines provide recommendations on doses.[6]

Typically, it is recommended to give 60 Gy in 30 fractions over 6 weeks to the site of resected disease; for patients with smaller lesions, or in cases where shorter fractionation is preferred and optimal long-term cosmesis is not a clinical priority, there is the option of hypofractionated schedules, in which radiotherapy is given as a dose of 50 Gy in 20 fractions over 4 weeks or as 45 Gy in 15 fractions over 3 weeks. In the presence of positive microscopic margins, a dose of 66 Gy in 2 Gy fractions may be recommended.

For resected regional node disease in the presence of ECE, the NCCN guidelines recommend a dose of 60 Gy to 66 Gy in 30 to 33 fractions over 6.0 to 6.6 weeks; when ECE is not present, the guidelines recommend a dose of 56 Gy to 60 Gy in 28 to 30 fractions over 5.6 to 6 weeks.[6]

In the TROG 05.01 study, the recommended dose/fractionation to the surgically perturbed neck in the absence of disease was 54 Gy in 27 fractions over 5.5 weeks and, for the surgically unperturbed elective neck, the recommended dose/fractionation was 50 Gy in 25 fractions over 5 weeks.

CONCLUSION

Evidence, mainly from retrospective series, has identified adverse prognostic factors that predict for locoregional relapse in patients with NMSC; however, there is a lack of confirmatory prospective data examining the benefit of adjuvant RT in these patients. And although there is strong retrospective data supporting the role of adjuvant RT in high-risk disease—for example, in disease with metastatic regional nodal involvement—the data is less certain about the ways in which adverse features and the extent of disease should factor into the consideration of treatment with adjuvant RT. As a result of this uncertainty, the use of adjuvant RT in the treatment of NMSC is predominantly based on individual institutional policy. Further prospective studies in this area are warranted.

Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

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Merkel Cell Carcinoma: Emerging Biology, Current Approaches, and Future Directions

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OVERVIEW

Merkel cell carcinoma (MCC) is an aggressive neuroendocrine cutaneous cancer that predominantly occurs in patients who are older, and is associated with a high rate of distant failure and mortality. Current management strategies that incorporate surgery and radiotherapy achieve high rates of locoregional control, but distant failure rates remain problematic, highlighting the need for new effective systemic therapies. Chemotherapy can achieve high response rates of limited duration in the metastatic setting, but its role in definitive management remains unproven. Recent developments in our knowledge about the biology of MCC have led to the identification of new potential therapeutic targets and treatments. A key finding has been the discovery that a human polyomavirus may be a causative agent. However, emerging data suggests that MCC may actually be two distinct entities, viral-associated and viral-negative MCC, which is likely to have implications for the management of MCC in the future and for the development of new treatments. In this review, we discuss recent discoveries about the biology of MCC, current approaches to management, and new therapeutic strategies that are being investigated.

Merkel cell carcinoma is an uncommon neuroendocrine carcinoma that mostly arises in sun exposed areas, with the head and neck being the most frequent site. There is geographic variation in incidence with higher rates in Australia than in the United States.[1,2] It predominantly occurs in patients who are older, with onset occurring at a median age of 75 to 80, and it is more common in males.[1,2] Recognized risk factors are ultraviolet (UV) sunlight exposure and immunosuppression, and more recently, the Merkel polyomavirus (MCV) has been identified as a causative agent.[3]

Pathologically, MCC has features of a trabecular neuroendocrine carcinoma arising from Merkel cells, which act as sensory touch receptors in the basal layer of the epidermis.[4,5] A diagnosis of MCC from small cell lung cancer is challenging based on morphology alone, but can often be distinguished by the presence of CK20 and absence of TTF-1 with immunohistochemical (IHC) staining.[6] Approximately 15% of MCCs are diagnosed at the metastatic stage without evidence of a primary and appear to be associated with a better prognosis.[7] Heath et al have recently defined the clinical features that may serve as clues to the diagnosis, summarized by the acronym AEIOU: asymptomatic/lack of tenderness, expanding rapidly, immunosuppression, older than age 50, and UV exposed site on a fair-skinned person.[8]

BIOLOGY

Merkel Cell Polyoma Virus

A higher risk of developing MCC in patients who are immunosuppressed provided a strong impetus to search for a viral etiology in MCC. The search for viral sequences in tumors was subsequently enabled by the development of deep transcriptome sequencing, which led to the seminal discovery of the MCV in 2008.[3] Despite the now clear oncogenic role of the virus, MCV is likely to be part of normal skin flora, as viral DNA can frequently be detected at low levels in the normal skin of healthy individuals.[9] This is further supported by serologic studies showing that children can be infected by MCV from a very young age and that up to 80% of adults in North America have been exposed to the virus by age 50.[10] MCV is a double-stranded DNA virus that harbors large and small-T antigens (LT; ST) required for modulation of the host cell and viral replication. The oncogenic potential of MCV is thought to only occur on chance sequential events of clonal integration into the host genome and then acquisition of mutations in the 3′ end of the LT. Mutations in the LT truncate the C-terminus of the oncoprotein, disrupting the helicase domain, which renders the virus replication incompetent. This may be important for several reasons, but primarily to prevent cell death through inappropriate DNA replication at integration sites, which would lead to

replication-fork collisions and DNA-strand breakage.[11] Importantly, the mutation does not affect the functional ability of LT to sequester the retinoblastoma protein (RB), a cell cycle regulator and tumor suppressor that is frequently disrupted in cancer.

Continuous expression of T-antigens have been shown to be required for maintenance of MCV-positive cell lines.[12] However, unlike the related and intensively studied simian vacuolating virus 40 (SV40), the expression of MCV LT alone does not appear to be sufficient to transform cells, which is in contrast to the MCV ST, which has more potent oncogenic potential.[13] MCV ST has been shown to act downstream of mTOR in the PI3K/AKT/mTOR signaling pathway, preventing dephosphorylation of 4E-BP1, which regulates cap-dependent translation of mRNAs.[13] More recently, the MCV ST has been shown to bind to cellular FBXW7, which is a subunit of the SKP1/CULLIN1/F-box (SCF) protein ubiquitin ligase complex that negatively regulates the LT and other cellular proto-oncogenes such as cMYC and cyclin E.[14] A transgenic mouse harboring MCV ST driven by a bovine keratin 5 promoter has been recently described (K5-ST). Induction of K5-ST in adult mice resulted in epidermal transformation and squamous cell carcinoma in situ. The mice, however, failed to develop MCC, which indicates there is perhaps a requirement of both LT and ST expression or that targeted expression is required in an alternative Merkel cell precursor cell type. Development of an immunocompetent MCC animal model would be an invaluable research tool for the preclinical evaluation of novel therapies.

Viral-Negative MCC

In Europe, the United States, and Japan, the frequency of cases with MCV is variable, but generally thought to be approximately 80% of MCC tumors.[15] This still leaves a substantial fraction of viral-negative cases with a relatively unknown biology. Clues to the underlying origins of viral-negative tumors can be drawn from observations in different geographic regions. In Australia, the association of MCV infection with MCC appears to be much lower. Three independent studies from major Australian cities report a frequency of 18% to 24%,[15-17] with the exception being a study from Sydney reporting a similar frequency to that found in Germany (80%).[18] Variability in the reported prevalence of viral-associated MCC between studies has been attributed to the choice of the individual antibody used for IHC detection of viral LT expression in tumors.[19] However, the difference between studies in Australia and the Northern hemisphere would appear outside the expected variance between IHC assays. Furthermore, IHC and polymerase chain reaction detection of viral DNA have both been used in Australian studies and these assays have been shown to be mostly concordant.[20]

A higher prevalence of MCC in the Australian population with a predominance of viral-negative tumors suggests that excessive sun damage is likely key to the pathogenesis of the viral-negative subtype. Potential mechanisms explaining increased risk associated with sun damage could involve combined effects of localized immune suppression and the strong mutagenic effects of UV-mediated DNA damage.[21] A telling indicator of UV damage is the DNA mutation signature involving C to T transitions at dipyrimidine bases (i.e., CC to TT) frequently observed in skin cancers such as melanoma.[22] Importantly, these types of mutations have been identified in MCC tumors through sequencing the *TP53* tumor-suppressor gene.[23]

Further cumulative evidence to support the notion of two subtypes includes the histologic, clinical, and molecular differences that have been observed between viral and nonviral MCC. MCV-positive and -negative tumors have been reported to have specific morphologic differences.[24] Viral status has also been associated with different growth properties of the respective cell lines.[11] Gene expression profiling can also broadly cluster MCC tumors, which is predominantly driven by an elevated immune signature in the viral-positive group.[25] A poorer prognosis has been associated with viral-negative MCC in some studies, although this has not been consistently demonstrated in different patient cohorts.[17,18,26-29]

Genetic differences observed between MCC tumors based on viral status can be explained in part by the convergent, yet distinct mechanisms for disruption of common pathways. As previously mentioned, the tumor-suppressor protein RB is a key target of the polyoma virus LT.[30] Viral-negative tumors show low to absent protein expression of RB[20] and *RB1* copy number loss and loss-of-function mutations account for genetic disruption in a large proportion of viral-negative MCC tumors.[31-33] Pathogenic mutations in *TP53* and overexpression of the p53 protein (commonly associated with *TP53* mutation), also appear to be largely restricted to viral-negative tumors.[20] Curiously, unlike SV40, the MCV LT is not thought to directly regulate p53 and therefore may be altered through an indirect mechanism.[34] Oncogenic muta-

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KEY POINTS

- Merkel cell carcinoma is an uncommon aggressive neuroendocrine cutaneous malignancy that predominantly occurs in patients who are older and is associated with a high rate of distant failure and death.
- Current management strategies that incorporate surgery and radiotherapy achieve high rates of locoregional control.
- Progress has been hampered by the lack of high-quality evidence, with current management strategies largely derived from retrospective studies.
- Merkel cell polyomavirus has been identified as a causative agent, but emerging data suggests MCC may be two distinct entities, viral-associated and viral-negative.
- Recent developments in our knowledge about the biology of Merkel cell carcinoma have led to the identification of new potential therapeutic targets and clinical trials investigating novel treatments including immunotherapeutic approaches.

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tions in *PIK3CA* predominantly occur in viral-negative tumors, although most MCC cancers regardless of viral status show activated PI3K/AKT signaling and are responsive to PI3K and dual PI3K/mTOR inhibitors.[35,36]

Despite evidence for the aberrant expression of common oncogenic and tumor suppressor pathways in MCC, the search for somatic mutations in other known cancer genes has revealed few tangible leads to date.[37] Genome-wide copy number analysis has revealed recurrent large regions of chromosomal gain and loss with more alterations observed in viral-negative tumors.[31] Focal high-level amplification of 1p34 harboring the *MYCL1* oncogene is a striking feature in approximately 40% of MCC cases, highlighting an interesting molecular parallel to small cell lung cancer.

A general paucity of new cancer gene discoveries in MCC may reflect the focused interrogation of just a few genes and the small sample sets analyzed to date. Furthermore, given the already potent oncogenic potential of MCV, it is plausible that this disease subtype is genetically quite simple and does not require additional cooperative gene mutations. Focused interrogation of the viral-negative group, which is ostensibly driven by mutagenic effects of sun damage, could be more informative from a genetic perspective and it will be interesting to search for convergence involving mutations in genes targeted by viral LT and ST. A "genomic landscape" interrogation of MCC by massively parallel (next-generation) sequencing is therefore clearly required.

MANAGEMENT OF MCC

The main aim of current treatment strategies is to obtain locoregional control without inducing unnecessary toxicity. Cases should be managed in the context of a specialized multidisciplinary team to ensure care can be individualized and all potential treatment modalities considered.

Optimal management of MCC is a therapeutic challenge in part because of its rarity and lack of high-quality evidence to direct treatment. Although we can extrapolate management principles from other skin cancers, such as melanoma and squamous cell carcinoma, MCC differs importantly from these conditions by being extremely sensitive to radiotherapy.

Potential treatment paradigms have been published previously, are readily available, and include the 2015 National Comprehensive Cancer Network (NCCN) guidelines.[38] In this review, we highlight recent developments and some of the differences in approach to the management of MCC.

Staging

MCC is associated with high rates of early nodal and distant metastatic spread. Relapse in nodal stations reportedly occurs in up to 76% of cases[39-42] and is associated with a substantial reduction in survival.[43,44] Effective staging of nodal and distant metastatic disease at diagnosis is essen-

tial. Previously, this has been limited to diagnostic CT scanning, but in recent years other useful staging modalities have emerged.

PET. MCC exhibits high fludeoxyglucose (FDG) avidity on PET scanning,[45,46] permitting the detection of involved subcentimeter nodes that may not be appreciated on the initial CT.[47] Although there are no published multicenter, prospective studies evaluating FDG PET/CT in MCC, there are many retrospective, single-institution studies that have suggested that FDG PET may have a role, as most studies have found that PET changes stage and management in up to 30% of patients.[48-50] The largest study published to date from the Peter MacCallum Cancer Centre assessed 102 consecutive patients who were staged with PET/CT, which resulted in changed staging in 22% of patients and management in 37% of patients.[50] On multivariable analysis of prognostic factors, PET stage was associated with overall survival. In general, these studies were too small to report the positive and negative predictive value, but a recent systematic review of the literature suggested that PET/CT has a sensitivity of 90% and a specificity of 98% in detecting MCC.[51]

Although there has been no clear evidence to date that PET/CT staging will substantially change clinical outcomes for patients, a change in stage and treatment intent (and/or modality) in up to 30% of patients warrants its inclusion in to the current NCCN guidelines as a potential staging tool. In our department, PET/CT staging is recommended for all patients with T2 or clinically node-positive disease. An ongoing study being conducted by the Trans-Tasman Radiation Oncology Group (TROG) is prospectively evaluating the role of PET/CT in a multicenter trial of patients with MCC (ClinicalTrials.gov identifier NCT01013779).

Sentinel lymph node biopsy (SLNB). SLNB has become a standard tool in the nodal staging of MCC in many centers. SLNB detects lymph node spread in up to one-third of patients whose tumors would have otherwise been staged as N0.[52] MCC series data indicate an SLN positivity rate of 20% in T1 tumors, and 45% to 50% in T2 lesions.[52,53] Primary tumor factors such as size, depth of invasion, and lymphovascular invasion may be prognostic, but this has not been demonstrated conclusively.[54] In a large analysis of prognostic factors in 5,823 patients with MCC, investigators found that pathologic evaluation of node involvement was substantially better at prognosticating with regard to survival compared with clinical/radiologic examination alone.[55] Certainly, SLNB in MCC appears to be able to detect microscopic nodal spread and is prognostic for survival.

Most series indicate that patients with SLNB-positive disease receive treatment to the nodal region. Regional relapse rates following treatment in this setting are very low.[42,54,56] However, in the setting of a negative SLNB result, it is less clear whether prophylactic treatment can be omitted. The false-negative rate of SLNB has been re-

ported to be 10% to 20%.[54,55,57] This may be particularly problematic in the head and neck region where SLNB may be less accurate as a result of the complex and variable lymphatic drainage, postoperative tissue changes, and the presence of more than one sentinel lymph node.

SLNB has been recommended as a standard procedure for the staging of patients with MCC in the NCCN guidelines.[38] This is not unreasonable, but patients should be carefully selected for the procedure in light of the limited evidence of efficacy in some settings (postreconstructive surgery, immunosuppressed patients, or high-risk lesions). In our department, patients with lesions larger than 2 cm are considered sufficiently high risk to warrant prophylactic nodal irradiation, regardless of a SLNB result and so it is not recommended. For patients with tumors smaller than 2 cm, we will recommend SLNB in patients with tumors larger than 1 cm and is planned as part of their initial surgery. In patients with lesions smaller than 1 cm, we make an individual assessment based on risk factors. Further studies are required to better define the benefit and utility of SLNB.

Definitive Management

Stage I and II disease (node-negative).
Treatment in stage I and II MCC generally involves surgical resection of the primary tumor with clear margins followed by adjuvant radiotherapy. However, it is not necessary to obtain wide or even clear surgical margins if this would compromise cosmesis or function, or delay planned adjuvant radiotherapy.[38,58,59] Adjuvant radiotherapy provides superior locoregional control rates compared with surgery alone.[43,60-62] Patients with very small primary tumors (< 1 cm), or negative SLNB with clear margins and no adverse features, such as lymphovascular invasion and immunosuppression, may be able to avoid adjuvant radiotherapy.[63] If surgery is not feasible or refused, definitive radiotherapy can achieve high rates of locoregional control. Veness et al reported a 3-year locoregional control rate of 75% with radiation alone in a population with poor prognosis, but overall 60% of patients relapsed, most commonly outside the radiation field.[64]

Stage III disease (node-positive).
Stage IIIA disease (microscopic nodal) is usually detected via SLNB, and treatment of the nodal basin is recommended with radiotherapy or lymphadenectomy. Both modalities achieve excellent results,[56] with radiotherapy permitting concurrent adjuvant treatment to the primary site.

In IIIB disease, clinically evident node disease can be treated with lymphadenectomy and radiotherapy, or definitive radiotherapy. The NCCN guidelines recommend initial surgery as the standard therapy in this setting,[38] although a different approach may be adopted, particularly for MCC localized to the head and neck. Radiotherapy alone has been shown to provide good regional control of gross node disease, with isolated regional recurrence being uncommon.[56,65,66] The MD Anderson Cancer Center has recently reported its experience with radiotherapy in MCC localized

in the head and neck with 96% local and regional control rates, and notably no regional recurrences in 22 patients with gross nodal disease who were treated with radiation alone.[65]

If IIIB disease is treated surgically it is likely that the majority of patients would be recommended for postoperative radiotherapy based on multiple nodes or extracapsular extension. Decisions about the optimal approach must take into account the lack of evidence that bimodality treatment is more effective in achieving regional control than radiotherapy alone, as well as the predominant distant pattern of failure, and the additional toxicity and effect on quality of life associated with bimodality treatment.

In view of the high risk of distant metastases, and the similarities to small cell carcinoma of the lung, there has been interest in incorporating chemotherapy into the definitive management of patients at high risk. The TROG 96.07 trial evaluated the treatment of 53 patients with high-risk local and nodal MCC with radiotherapy and four cycles of carboplatin and etoposide.[67] Radiotherapy doses were moderate (50 Gy/25 fractions), and the bulk of disease treated ranged from microscopic to lesions larger than 5 cm. Gross node disease was present in 62% of patients. The 3-year overall survival, locoregional control, and distant control was 76%, 75%, and 76%, respectively. However, a high febrile neutropenia rate was observed that predominantly occurred during the peak of the radiation skin reaction. A subsequent trial demonstrated that giving weekly carboplatin during radiation followed by adjuvant carboplatin and etoposide was much better tolerated.[68] However, the single arm design of these trials does not permit any definitive conclusions about efficacy. Retrospective comparisons to patients treated with radiation alone have yielded mixed results with some studies finding no evidence of benefit, whereas a recent analysis restricted to head and neck primaries has suggested improved overall survival with chemoradiation. The role of chemotherapy in this setting remains unproven, and could only be established by a randomized trial.

Stage IV disease (distant metastases).
Distant metastases develop in 20% to 30% of patients with MCC.[50,65,69,70] The mainstay of anticancer management of metastatic MCC has been chemotherapy, which achieves high response rates (60% to 75%), but of limited duration. Based on apparent similarities to small cell carcinoma, regimens such as platinum and etoposide or cyclophosphamide, doxorubicin, and vincristine are most commonly used for first-line chemotherapy.[71] However, there is limited evidence to guide decision making, with no randomized trials evaluating different regimens, and limited data about the effect of chemotherapy on survival, symptom benefit, or quality of life. Bearing in mind that patients are frequently older with comorbidities, many patients are not good candidates for chemotherapy and are best managed by supportive care alone.

NEW TREATMENTS

The viral etiology and an epidemiologic link to immunosuppression suggest that immunotherapies may be effective in

treating MCC tumors. Many MCC tumors elicit a strong immune response with brisk infiltrates of intratumoral CD8+ T-cells (TILs), which is an independent indicator of better survival.[72-74] Viral-antigen specific CD8+ T-cells can also be detected in the peripheral blood of patients with MCC and fluctuate in response to treatment.[75] Antibody blockade of immune checkpoint receptors and ligands, such as CTLA-4 and PD-1/PD-L1 that reactivate cytotoxic T-cell activity, have demonstrated durable responses in the treatment of refractory solid tumors.[76,77] Importantly, viral specific T-cells in MCC express PD-1 and high tumor specific expression of the ligand PD-L1 has been observed in viral-positive, but not viral-negative tumors.[75,78] Phase II trials using anti-PD-L1 (MSB0010718C; NCT02155647), anti-PD-1 (pembrolizumab; NCT02267603), and anti-CTLA-4 (ipilimumab; NCT02196961) are currently open. An alternative or complementary immune strategy is adoptive immunotherapy, which involves the isolation of tumor-specific autologous T-cells from a patient, which are then cultured in vivo and infused back into the patient. This strategy has proven effective for treating melanoma.[79] Methods have been described for the isolation of MCV-specific cytotoxic T-cells from patients with MCC,[80] and a phase I/II clinical trial using autologous T-cell therapy with aldesleukin is currently underway (NCT01758458).

Targeting dysregulated cell growth and proliferation pathways within MCC tumors present another potential therapeutic avenue. MCC tumors overexpress receptor tyrosine kinases such as cKIT, PDGFR, and VEGFR2.[81-83] Despite promising early preclinical evaluation of imatinib (targeting KIT and PDFGR), a low response rate was observed in a clinical trial, although a complete response has been reported elsewhere.[84] The multikinase inhibitor pazopanib targets receptor tyrosine kinases, including cKIT, FGFR, PDGFR, and VEGFR, and a complete response to this drug has been observed in MCC resistant to cytotoxic therapy.[85] A phase II trial of pazopanib in patients with neuroendocrine tumors including MCC is currently open (NCT01841736). Cabozantinib, which targets VEGFR2/cMET, is being investigated in a phase II MCC trial (NCT02036476). As previously mentioned, MCC tumors may be responsive to inhibition of the PI3K/AKT/mTOR axis, and a number of clinical trials are currently active for treatment of solid tumors using PI3K inhibitors.

A low level of apoptosis is a feature of MCC. BCL-2, a prosurvival member of the intrinsic apoptosis pathway, is overexpressed in approximately 80% of MCC tumors.[86] Oblimersen sodium (G3139), a phosphorothioate antisense oligonucleotide that targets BCL-2, demonstrated good efficacy in a preclinical assessment,[87] but proved ineffective in patients with MCC.[88] The orally available drug ABT-263, which targets multiple BCL-2 family members, has also demonstrated preclinical activity against MCC cell lines by inducing apoptotic death.[89] Theoretically, ABT-263 may be more effective than G3139 in patients, given that it targets multiple BCL-2-family members. Survivin is a member of the inhibitor of apoptosis family and is upregulated by MCV LT.[90] High survivin expression corresponds with an aggressive clinical course and poor prognosis in patients with MCC.[91] Survivin expression can be attenuated using sepantronium bromide, also called YM155.[92] Treatment of MCC xenografts with YM155 demonstrated cytostatic response in MCC xenografts; however, this has yet to be tested in patients with MCC.[93]

The somatostatin receptor type 2 (SSTR2) is expressed in 90% of MCC tumors.[94] Somatostatin analogs such as octreotide bind to SSTR2 and elicit antiangiogenic, antisecretory, and antiproliferative responses in functional and nonfunctional neuroendocrine tumors.[95] Long-term response to octreotide has been reported in MCC,[96] and a French phase II trial testing the efficacy of the drug lanreotide is about to begin (NCT02351128). Peptide receptor radionuclide therapy (PRRT) involves covalent attachment of radioactive isotopes to somatostatin peptide analogs (e.g., $_{177}$lutetium octreotide). Given the exquisite radiosensitivity of MCC cells, there is a strong rationale for using PRRT in MCC. There have been several case reports demonstrating responses to PRRT used alone or with chemotherapy.[97-99]

Other biologically-targeted therapeutic strategies involve the use of antibody-drug conjugates and immunocytokines. Most MCC tumors demonstrate cell surface expression of CD56 (NCAM).[100] Lorvotuzamab mertansine (IMGN901) is a conjugate of a humanized anti-CD56 antibody with maytansinoids, such as DM1 (a microtubule targeting agent). The drug IMGN901 has showed efficacy against MCC in early phase trials and has been granted orphan status by the U.S. Food and Drug Administration (FDA). The immunocytokine F16-interleukin (IL)-2 is the fusion of the monoclonal antibody fragment F16 specific to tenascin-C fused to IL2. Tenascin-C is an angiogenesis marker and expressed in the reactive stroma of many solid tumors, whereas IL-2 is a potent immune stimulator. Preclinical studies have shown efficacy in human xenograft models of breast carcinoma and glioblastoma,[101,102] and phase IB and II trials in solid tumors and breast cancer have shown the drug is well tolerated and efficacious in some patients. A phase II trial using F16-IL2 in combination with paclitaxel for metastatic MCC is currently underway (NCT02054884).

CONCLUSION

Current management strategies achieve high rates of locoregional control, but distant failure rates remain problematic. Management of metastatic disease is challenging; chemotherapy can achieve high response rates of limited duration and is often associated with toxicity in this older population. The recent upsurge in our understanding of the biology of MCC is opening up new potential therapeutic targets and treatments. Finally, the recognition that MCC may be two distinct entities, viral-associated and viral-negative MCC, is likely to have implications for the management of MCC in the future and for the development of new treatments, somewhat analogous to oropharyngeal cancer following the identification of the HPV as a causative agent.

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Relationships are considered self-held and compensated unless otherwise noted. Relationships marked "L" indicate leadership positions. Relationships marked "I" are those held by an immediate family member; those marked "B" are held by the author and an immediate family member. Institutional relationships are marked "Inst." Relationships marked "U" are uncompensated.

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Locoregional Therapies in the Setting of Systemic Treatment Advances: What's Next?

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Perfusion and Infusion for Melanoma In-Transit Metastases in the Era of Effective Systemic Therapy

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OVERVIEW

The management of melanoma in-transit metastases (IT-mets) is challenging. For many years, the absence of effective systemic therapy has prompted physicians to focus on regional therapies for melanoma confined to the limb. The introduction of isolated limb perfusion (ILP) and isolated limb infusion (ILI) has enabled effective delivery of cytotoxic drugs in an isolated circuit, so as to overcome systemic toxicity and maximize local response. Both techniques have evolved over years and both tumor necrosis factor (TNF)-alpha–based ILP and ILI have distinct indications. The development of new systemic treatment options for patients with melanoma in the past decade has shed a new light on melanoma therapy. The present manuscript focuses on the modern role of ILI and ILP in the treatment of patients with melanoma with in-transit metastases in the era of effective systemic therapy. The response and control rates of ILI/ILP are still superior to rates achieved with systemic agents. The extent of disease in patients with stage III disease, however, warrants effective systemic treatment to prolong survival. There is great potential in combining rapid response therapy such as ILI/ILP with systemic agents for sustainable response. Trial results are eagerly awaited.

Melanoma incidence in the United States has increased during recent decades to an estimated number of 76,100 new cases in 2014,[1] comprising 4.6% of all new cancer cases. In approximately 5% to 8% of these patients, IT-mets will develop during the course of the disease. These IT-mets are a result of tumor emboli trapped within the dermal and subdermal lymphatics and can occur anywhere between the site of the primary tumor and the draining regional lymph node basin. The management of these IT-mets is challenging, as they are often numerous and can be bulky. The median time between diagnosis of the primary tumor and the development of IT-mets is between 13 months and 16 months. If a patient develops IT-mets, this is often a prelude to the appearance of systemic disease. In the current American Joint Committee on Cancer Melanoma Staging and Classification, patients with IT-mets are staged N2 or N3, depending on associated lymph node metastases. The corresponding 5-year survival rates are 69% and 52%, respectively.[2]

Various treatment options exist for melanoma IT-mets, as the presentation can range from very few and tiny lesions easily amenable to local excision, to more than 100 and extremely bulky lesions in previously extensively treated extremities. This wide range of clinical presentation demands a tailored approach for each patient. Whereas, in some patients, resection of limited disease is part of a curative approach, other patients may need treatment of their IT-mets even in the presence of stage IV disease for palliative reasons.

The treatment of these IT-mets can therefore be challenging, especially when the interval between new lesions is short, when numerous and bulky metastases are present, or when multiple treatment modalities have already been applied and failed. It is in this context that Creech and Krementz developed the concept of ILP in 1958.[3]

ILP TECHNIQUE

Until recently, melanoma was infamously refractory to any kind of systemic treatment. This resistance stimulated the search for techniques that could deliver high concentrations of chemotherapy or other agents to the affected limb, without the risk for systemic toxicity. In this way, drug concentrations would potentially suffice to achieve antitumor effect. As IT-mets of extremity melanomas are, per definition, confined to a limb, isolation of the affected limb from the systemic circulation would offer such an opportunity. This isolation can be achieved by surgical access to the artery and vein on either iliac, femoral, popliteal, axillary, or brachial level. The artery and vein are clamped and cannulated after which the catheters can be connected to a heart-lung machine to get an oxygenated circuit. To further isolate the limb, a tourniquet is placed proximal to the site of the perfusion. Melphalan (L-phenylalanine mustard) has been the standard drug used in ILP because of its efficacy and toxicity profile.[4] Drug concentrations in the limb are 20-times higher than can be achieved

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systemically using this isolated circuit. Melphalan concentrations of 10 mg/L (leg) or 13 mg/L (arm) are considered standard dosages. The major concern of ILP is potential leakage of the effective agents to the systemic circulation. Therefore, leakage monitoring is mandatory and a precordial scintillation probe is placed to detect any radioactively labeled albumen administered to the isolated circuit that has potentially leaked to the systemic circulation.

Melphalan-based ILPs have been used for decades in the previous century as complete response (CR) rates of 40% to 50% and overall response rates of 75% to 80% were achieved, unmet by any other treatment modality.

ILP MODIFICATIONS

Since the introduction of ILP, many modifications have been applied to improve tumor response. These modifications have led to an improved insight in the optimal temperature, the optimal drugs, and the optimal indications for the procedure.

Temperature

Temperature of the perfused tissue is important in more than one way. The temperature of the skin has to be warmed during perfusion to prevent vasoconstriction in the dermal and subdermal tissues. Especially in superficial IT-mets, application of a warm water mattress can improve the local drug delivery as the uptake of the drug by in-transit metastases in vivo has proven to be twice as high at 39.5°C than at 37°C.[5] The second reason for hyperthermia is the idiosyncratic sensitivity of tumor cells to heat. Moreover, hyperthermia can improve the uptake of the drug in tumor cells, especially at temperatures greater than 41°C.[6,7] However, hyperthermia is associated with increased local toxicity. Tissue temperatures of 41.5°C to 43°C during ILP can yield high response rates,[8] but the local toxicity of these procedures can lead to major complications and even amputation of the perfused limb.[9]

KEY POINTS

- Therapy for patients with extensive melanoma in-transit metastases should be effective in providing local control.
- Tumor necrosis factor-based isolated limb perfusion (TM-ILP) is effective in the treatment of bulky melanoma in-transit metastases; isolated limb infusion (ILI) is effective in the treatment of lower-burden disease.
- Modern TM-ILP and ILI treatment is safe.
- New systemic agents for melanoma treatment have changed the treatment of patients with stage IV melanoma drastically, but response and local control rates do not reach ILI/ILP standards.
- Combination of ILI/ILP to induce rapid local response, followed by effective systemic therapy to increase overall survival, has great potential to become standard therapy in patients with extensive melanoma in-transit metastases.

The use of true hyperthermia should therefore be avoided. Mild hyperthermia for ILP is used as a compromise between response and toxicity.

Drugs

Several attempts have been made to improve the response on ILP by using other cytostatic drugs than melphalan. Commonly used drugs in the treatment of systemically metastasized melanoma, either alone or in a combination schedule, are dacarbazine and cisplatinum. Therefore, among others, these drugs were tested in the ILP-setting, but no drug or drug combination used for patients with melanoma has proven to achieve results superior to melphalan.[4,10] Probably the only alternative schedule still in use is the combination of melphalan and actinomycin-D.[11]

Probably the most influential adjustment of ILP has been the introduction of TNF by Lejeune and Liénard in 1988. TNF was isolated as an endogenous factor, especially active in inflammation, with necrotizing ability on tumor cells.[12] We now know that TNF has a dual mechanism of action: the direct cytotoxic effect of high-dose TNF to tumor cells certainly plays a role in antitumor activity,[13] but more importantly the TNF effect on the so-called tumor-associated vasculature induces a rapid change in tumor morphology characterized by hemorrhagic necrosis.[14] However, the systemic application in patients with melanoma was very disappointing.[15] TNF turned out to be a potent mediator in septic shock and, therefore, the systemic side effects (acute drop in vascular resistance leading to low blood pressure, fever, etc.) were the major factors hindering systemic application of this cytokine.[16] The maximum tolerated dose of TNF in humans turned out to be 10-times to 50-times lower than required for antitumor effect,[17] so that systemic, but also intralesional administration of TNF, was not clinically applicable. The concept of ILP combines the advantages of the TNF antitumor activity with the avoidance of systemic effects. Moreover, the cytotoxic effects of TNF are known to be enhanced in hyperthermic conditions and with the addition of alkylating chemotherapeutics,[18,19] both prerequisites already existing in the ILP model. The reintroduction of TNF in anticancer therapy by application in the ILP protocol combined optimal activity with minimal toxicity.[20]

Indications

The success of ILP in the treatment of melanoma IT-mets has prompted trials to test the efficacy of ILP in the adjuvant setting after excision of the primary melanoma. After the first disappointing results, this indication was largely abandoned by most melanoma centers.[21] Recently, the long-term results of a Swedish trial were published that affirmed the conclusion that adjuvant ILP after excision of high-risk primary melanomas does not improve survival of these patients.[22] Another plausible thought has been the repetition of perfusion soon after the first ILP, the so-called double perfusion schedule. The premise that repeated administration of chemotherapeutic agents is more effective than single use is adopted from the systemic chemotherapy situation and is based on the idea

that residual tumor cells after the first treatment may be eliminated and that partially damaged tumor cell after first exposure may be more vulnerable to chemotherapy on repeated exposures. In the ILP situation, the double perfusion schedule (interval 3 to 4 weeks, second perfusion with reduced melphalan dose, normothermic ILP) led to higher CR rates than single ILP,[23] but the median duration of response was not altered. Fractioning of melphalan administration and the use of true hyperthermia have been used in a double perfusion schedule in which a true hyperthermic perfusion with no chemotherapeutic agents was followed by a normothermic melphalan-ILP 1 week later. The achieved response rates with this protocol are high, probably because of the synergistic effect of hyperthermia and melphalan, whereas, because of to the fractioning, no increased toxicity was observed compared with single ILP.[24] It was postulated that the double perfusion schedule could be an alternative for a TNF-based ILP. In the TNF era, no further trials of repeat ILPs at short intervals have been conducted.

ISOLATED LIMB INFUSION

In the early 1990s, ILI was developed by Thompson et al at the Melanoma Institute Australia (MIA, formerly Sydney Melanoma Unit) as a simplified and minimally invasive alternative to ILP.[25] This has been the most fundamental change in the concept of ILP, although the basic principles are very much alike. Both ILP and ILI involve a method of vascular isolation and perfusion of the extremity with cytotoxic agents. Drug concentrations in the isolated limb can be administered up to 10-fold of the maximum tolerated systemic concentration, and systemic side effects are avoided in both ILI and ILP.[26] Like ILP the primary indication for ILI is patients with inoperable in-transit melanoma of the extremity.

During ILI, arterial and venous catheters are inserted percutaneously. Using a standard Seldinger technique the catheters are placed via the contralateral femoral artery and vein in the disease-bearing limb. In the operating room, the catheters are connected to an extracorporeal circuit primed with saline solution, incorporating a heat exchanger but no mechanical pump or oxygenator. To achieve reliable isolation, a pneumatic tourniquet is inflated proximally around the affected limb. In this isolated circuit a low blood flow can be achieved by repeated aspiration from the venous catheter and reinjection into the arterial catheter using a syringe. The lack of oxygenation results in a hypoxic and acidotic environment. Great care is given to heating the limb, which is achieved by a heat exchanger in the external circuit, a warm-air blanket placed around the limb, and a radiant heater placed above it. The cytotoxic drug of choice for ILI is melphalan. At MIA and most other ILI centers, actinomycin-D is used additionally because of the satisfactory results with the combination, without negative effects on toxicity. After infusion of the drugs, the blood in the isolated circuit is circulated for 30 minutes. Since the half-life of melphalan is 15 minutes to 20 minutes and both melphalan and actinomycin-D are quickly absorbed by the tissues, a relatively short circulation time of 30 minutes is sufficient.[26-28] During ILI real-time leakage control of the cytotoxic drugs to the systemic circulation is not required because of the low flow and low pressure in the isolated limb circuit and the effective isolation reliably achieved by the pneumatic tourniquet. After 30 minutes the limb vasculature is flushed, after which normal circulation to the limb is restored by removing the tourniquet and the catheters.[29]

Differences between both procedures include that during ILI, no open surgical procedure is required, such as in ILP and arterial and venous catheters are inserted percutaneously. This results in a lower blood flow and in the isolated extremity during ILI (150 mL/minutes to 1,000 mL/minute for ILP vs. 50 mL/minute to 100 mL/minute for ILI). Furthermore, the ILI procedure is a hypoxic procedure, which leads to marked acidosis of the isolated circuit, in contrast to ILP where the pump oxygenator maintains the oxygenation in the limb. Catheter insertion via the contralateral groin for ILI is usually straightforward, even for a repeat procedure or after groin or axillary lymph node dissection; whereas, vascular access for ILP can be technically difficult. Finally, blood transfusion or more recently the use of autologous blood, which is required for ILP to prime the perfusion circuit, is unnecessary during ILI.[29]

RESPONSE ON ILP AND ILI IN PATIENTS WITH MELANOMA

As mentioned before, at the introduction of melphalan-based ILPs (M-ILP), the results of this treatment were unmet by any of the then available systemic medical treatments for melanoma. Overall response rates of greater than 80% were achieved in patients with IT-mets (Table 1). The enthusiasm for ILP was only tempered by two major objections: the procedure is fairly time-consuming and complicated, and, second, in bulky melanoma the response rates were relatively disappointing. The tumor bulk of the melanoma IT-mets can indeed be crucial as these are large, sarcoma-like lesions. The inhomogeneous drug uptake of soft tissue sarcomas was once the reason for abandoning M-ILP as a treatment option for these unresectable tumors.[30] The application of TNF to the M-ILP protocol (TM-ILP) in the sarcoma setting has changed this fundamentally, and TM-ILP is now used widely for this indication.[31] The bulky melanoma IT-mets resemble the sarcoma situation and this tumor bulk can indeed be crucial in appraising the TNF effect, as these large lesions benefit the most from the destruction of tumor associated-vasculature by TNF. This has led to comparative studies of M-ILP and TM-ILP. A randomized trial was published in 2006 comparing M-ILP and TM-ILP showing no beneficial effect of adding TNF.[32] This trial had extremely low CR rates compared with the available case series worldwide and the true indication of a TM-ILP protocol (bulky disease) could not be analyzed separately. Furthermore, the response rate in this trial was assessed at 3 months rather than at maximum response reached, which is usually after 3 months to 6 months. This has led to criticism and further series have been

TABLE 1. Response to Different Isolated Limb Infusion/Isolated Limb Perfusion Regimens

Regimen and Author	Year	No. of Patients		CR	PR	OR
Melphalan						
Klaase[60]	1994	120		64	25	89
Lingam[61]	1996	103		76	23	99
Aloia[62]	2005	58		57	31	88
Melphalan + Actinomycin-D						
Sanki[11]	2007	120		69	16	85
Melphalan ± TNF						
Noorda[33]	2004	90	TM-ILP	59	ns	ns
		40	M-ILP	45	ns	ns
Cornett[32]	2006	58	TM-ILP	26	43	69
		58	M-ILP	25	39	64
Alexander[34]	2010	43	TM-ILP	69*	26*	95*
		47	M-ILP			
Rossi[36]	2010	58	TM-ILP	61	29	90
		53	M-ILP	42	49	91
Hoekstra[35]	2014	39	TM-ILP	54	ns	93
		18	M-ILP	33	ns	84
ILI						
Kroon[41]	2008	185		38	46	84
Beasley[42]	2009	128		31	33	64
Wong[63]	2013	79		37	37	74
Coventry[43]	2013	131		27	36	63
Melphalan + TNF (since 2000)						
Di Philippo[37]	2009	113		63	25	88
Deroose[38]	2012	167		61	28	89
Olofsson[22]	2013	155		65	20	85

Abbreviations: CR, complete response; ILI, isolated limb infusion; ILP, isolated limb perfusion; PR, partial response; M-ILP, melphalan isolated limb perfusion; NS, not stated; OR, overall response; TM-ILP, application of tumor necrosis factor to M-ILP; TNF, tumor necrosis factor.
*Response rates are stated for the combined TM-ILP and M-ILP cohort.

published showing improved results of TM-ILP, albeit in a nonrandomized setting.[33-35] A retrospective mixed series of M-ILP and TM-ILP published by Rossi et al has shown a significantly improved CR-rate when TM-ILP was used.[36] The results of TM-ILP in a large series published after 2000 showed that CR rates are consistently reported to be slightly greater than 60%.[37-39] Overall, the view of most melanoma centers dealing with TM-ILPs is that true indications for TM-ILP is bulky disease or failure after previous M-ILP.[40]

The second issue of relative complexity is overcome by the application of ILP when appropriate. The most robust data of ILI are from Australia where since 1992 more than 400 melanoma ILIs have been performed at MIA. Following ILI a CR rate of 38% and a partial response (PR) rate of 46% are seen with a median duration of response of 22 months and 13 months, respectively.[41]

To date, two multicenter retrospective analyses have been published. In a U.S. study, 31% of the patients experienced a CR, 33% a partial response (PR), and 36% showed no response to the treatment.[42] Another multicenter study reported the responses in Australian centers, excluding MIA. They reported a CR of 27% and a PR of 36%.[43] Recently a systematic review was published including all the published ILI papers showed a CR in 33% of the patients and PR in 40%.[44] Overall the results of ILI are at the lower end of the spectrum of those reported after ILP. ILI, however, is performed in older and more medically compromised patients, both of which are statistically independent prognostic factors for an inferior response rate when compared with ILP. The fact that the indications for ILI and ILP within the patient population with melanoma IT-mets differ, makes a head-to-head comparison impossible and unnecessary.

LOCAL CONTROL AFTER PERFUSION

Although TM-ILP can achieve excellent response rates in patients with melanoma IT-mets, the nature of the disease determines that the patients in this very unfavorable population often experience local recurrent disease in the limb. Reported recurrence rates after perfusion are approximately 50%. The duration of response is sustained for longer than 1 year.[38] The management of limb recurrences after ILI/ILP is essentially the same as for IT-mets in general: local excision if technically feasible, but repeat perfusion in extensive disease. After a PR following ILI, or when recurrent lesions appear, simple local treatment of the remaining or recurrent lesions by excision, laser ablation, electrodesiccation, injection with rose bengal, or radiotherapy can be effective in obtaining local disease control. A recent study showed that resection of residual disease after ILI leads to similar disease-free survival and overall survival as a CR after ILI alone.[45] Both ILI and ILP can be repeated in select patients showing results comparable to the first procedure.[46,47]

SURVIVAL AFTER PERFUSION

Melanoma IT-mets have a relatively poor prognosis because of the extent of the disease. A local treatment option such as ILI/ILP cannot be expected to alter this as survival is dictated by the presence or appearance of systemic disease. Median survival of patients after a perfusion is approximately 2 years but interestingly, this is highly correlated with response on perfusion. In patients undergoing ILI/ILP, a CR after perfusion corresponds to a median survival of 53 months and 44 months, respectively.[38,41] This implies that a perfusion can select those patients with high response rates who apparently have a more favorable tumor biology.

TOXICITY OF PERFUSION

An area of concern in the field of perfusions is the toxicity that is associated with the procedure. This can be divided into

systemic toxicity because of leakage of the perfusate to the systemic circulation, and local toxicity of the treated extremity. In the situation in which ILPs are performed in specialized and experienced teams, clinically relevant leakage percentages of greater than 10% are extremely rare and median leakage should be 0%.[38] In ILI, systemic leakage is not an issue because of the low pressure of the perfusion system.[48] Local toxicity of perfusions is scored according to the Wieberdink classification.[49] A few modifications of the ILP have reduced the local toxicity significantly. Firstly, TNF dose is reduced. In the original series it was 3 mg to 4 mg TNF for leg perfusions and 2 mg for the arm; at present dosages of 2 mg and 1 mg are used, respectively. This modification has widely been accepted after a randomized trial in patients with sarcoma showed equal effectiveness of the low-dose perfusions but with decreased local toxicity.[50] The effect of low-dose ILPs on local toxicity could be affirmed in further case series of patients with sarcoma but proved to be of no influence in patients with melanoma.[38] Reasons for this difference are unknown. Another adjustment in ILP leading to less local toxicity is the tendency to perform more distal perfusions to reduce the perfused limb volume. This has a profound effect on local toxicity in both ILP and ILI procedures.[40,51] Major local toxicity (Wieberdink grade greater than 3) is seldom seen in ILI/ILP and is in recent reports 3% for both procedures. It can be concluded that ILP, and ILI to even a higher extent, are safe procedures with little and manageable toxicity. Perfusions have been performed safely in the older population and repeat procedures can be performed without increased toxicity.

ILI/ILP AND SYSTEMIC THERAPY

The poor survival after perfusion, despite the excellent regional response rates, raise the question of whether a local therapy such as ILI/ILP should still be used on a stand-alone basis in patients with extensive disease. In this light, a parallel can be seen in patients with positive deep pelvic lymph nodes. Both IT-mets and deep pelvic nodes reflect extensive disease and, recently, it has been shown that the extent of surgery to the deep pelvic and obturator nodes does not improve the outcome of these patients. In other words, the prognosis of these patients is dictated by the biology of the disease rather than by the extent of surgery.[52,53] The same mechanism is likely to be applicable to the IT-met situation. Until recently, response rates on systemic therapies were poor, and complete focus lied on treating the local situation. Fortunately, this situation has changed dramatically by the introduction of BRAF/MEK/KIT inhibitors, anticytotoxic T-lymphocyte-associated (CTLA) protein-4 antibodies and programmed death (PD)-1 pathway inhibitors.[54] Patients with stage IV melanoma experience response rates of approximately 50% and, in a subset of patients, long-term benefit can be obtained.[54] Although the majority of patients who entered the trials of these new drugs indeed had stage IV disease, most protocols allowed patients with unresectable stage III disease to enroll as well. The patient with IT-mets eligible for perfu-

sion has by definition unresectable stage III disease and, therefore, trial results can be extrapolated to this subset of patients, albeit with caution and in the awareness that response to ILP is dependent on stage of disease.[55]

It is, however, unlikely that systemic therapy will replace ILI/ILP in patients with extensive IT-mets. The response rates of the new agents are impressive compared with standard chemotherapy but are far below those that can be achieved with a perfusion. BRAF inhibitors have impressive and rapid response rates of approximately 60% (overall response) in patients with *BRAF* mutation. Drawbacks are numerous, however; the median duration of response is only about 7 months, after which resistance seems almost inevitable, there is a wide interpatient variability in response to treatment, and toxicity associated with BRAF inhibition cannot be neglected.[54] A more durable response can be obtained with anti-CTLA4 antibodies, but only a minority of patients will respond. Patients with multiple unresectable IT-mets will remain unresectable after a PR, so that the aim of therapy should ideally be CR. The CR rates of ILI and especially ILP of around 60% are still unmet by any systemic agent. The superior local control rate of a perfusion combined with the mild toxicity compared with systemic treatment mean that perfusion remains the optimal treatment option in these patients.

Although replacement of a perfusion by systemic therapy is unlikely in the near future, the development of new potent agents in the systemic treatment of patients with melanoma offers new possibilities in combining drugs. The first data on combining new systemic agents are encouraging with OR rates of 64%, a duration of response of 11 months, and a 1-year overall survival rate of 72% with the combination of a BRAF and MEK inhibitor.[56] BRAF inhibition followed by anti-CTLA4 therapy is also appealing, but this regimen has produced disappointing results in retrospective series.[54] The combination of two different ways of drug delivery (systemic and in the isolated circuit) is a logical next step. When systemic targeted therapies are administered in combination with chemotherapy administered by ILI, chemotherapy resistance can potentially be overcome by increasing the cytotoxic efficacy and, thereby, the responses.[57] In a multicenter phase II study combining melphalan ILI and systemic ADH-1, a cyclic pentapeptide that disrupts N-cadherin adhesion complexes, an overall response rate of 60% was achieved without increasing toxicity, compared with an overall response rate of 40% achieved previously with melphalan alone at the same institutions.[58] Improved responses were also seen when melphalan ILI was performed after systemic bevacizumab, a monoclonal antibody against VEGF causing increased delivery of melphalan to the tumor cells, in a preclinical melanoma model.[59] A clinical trial administering bevacizumab in combination with melphalan ILI is eagerly awaited. Currently, the use of the systemic anti-CTLA-4 antibody ipilimumab, before or after melphalan ILI, is being investigated in phase I and II trials (NCT01323517, NCT02115243).

Potentially more attractive is the combination of ILI/ILP for rapid response, followed by systemic therapy for survival bene-

fit. A phase II trial protocol is presently open for recruitment combining ILP and systemic ipilimumab (NCT02094391).

In conclusion, ILI and ILP are here to stay. The procedures provide rapid responses that are still superior to the responses achieved by systemic therapy, even in the latest trials. The responses are obtained at the cost of only very mild local, and vir-

tually absent, systemic toxicity. Patients with extensive IT-mets do need local treatment for disease control, but as unresectable stage III disease is a reflection of poor tumor biology, survival remains relatively poor. We firmly believe that this provides a massive opportunity for systemic agents. The results of the combination trials are awaited with great expectations.

Disclosures of Potential Conflicts of Interest

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Neoadjuvant Therapy for Melanoma: A Promising Therapeutic Approach and an Ideal Platform in Drug Development

Ahmad A. Tarhini, MD, PhD

OVERVIEW

Patients with locoregionally advanced but surgically operable melanoma continue to carry a high risk of relapse and death despite the best available standard management approaches. Neoadjuvant studies targeting this patient population tested chemotherapy with temozolomide and biochemotherapy (BCT), in which BCT demonstrated high tumor response rates but was eventually abandoned with the failure of BCT to deliver survival benefits in randomized trials of metastatic disease. Smaller neoadjuvant immunotherapy studies with interferon (IFN) alfa and ipilimumab have yielded promising clinical activity and important mechanistic insights and biomarker findings. Newer targeted and immunotherapeutic agents and combinations currently are being translated into the neoadjuvant setting at an accelerated pace and carry significant clinical promise. In drug development, the neoadjuvant approach allows access to blood and tumor tissue before and after initiation of systemic therapy, which allows for the conduct of novel mechanistic and biomarker studies in the circulation and the tumor microenvironment. Such studies may guide drug development and allow for the discovery of predictive biomarkers selected on the basis of their capacity to classify patients according to the degree of benefit from treatment or the risk for significant toxicity.

Survival of patients with melanoma varies widely by stage, from a potentially highly curable disease with surgery alone when detected in early stages to a disease with an overall guarded prognosis when it reaches advanced inoperable stages.[1] The American Joint Committee on Cancer divides cutaneous melanoma into four stages. Primary tumors confined to the skin and without regional lymph node involvement are assigned stages I and II depending on the thickness (depth) of the tumor, ulceration of the overlying epithelium, or mitotic rate. Stage III comprises a disease with clinical or pathologic evidence of regional lymph node involvement or the presence of in-transit or satellite metastases. Stage IV melanoma is defined by the presence of distant metastasis. Patients with stage I melanoma have an excellent prognosis with surgical treatment alone and a cure rate of more than 85%. The 5-year postsurgical survival rates in patients with stages IIA, IIB, and IIC disease are approximately 80%, 70%, and 50%, respectively, whereas the rates for patients with stages IIIA, IIIB, and IIIC disease are 78%, 60%, and 40%, respectively.[1-3] The apparently worse prognosis of patients with IIA and IIB disease according to the AJCC data may be attributed to the lack of adequate regional lymph node staging in some patients at a time when sentinel lymph node mapping was not widely adopted as a standard of care. For patients with stage IV melanoma, an historical median survival rate of approximately 6 months has significantly improved recently to rates that approach and exceed 1 year with new molecularly targeted agents (e.g., BRAF and MEK inhibitors) and immune checkpoint inhibitors (e.g., against cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] and programmed cell death protein 1 [PD-1]) that have made a real difference in the survival of these patients.[4-6]

LOCALLY AND REGIONALLY ADVANCED MELANOMA

Patients with stage III melanoma and clinically detectable regional lymph node involvement with or without in-transit metastases have a 5-year relapse rate of 68% to 89%.[7] The development of local or regional recurrence after initial surgical management portends an even poorer prognosis.[8,9] In the Melanoma Intergroup Surgical Trial, local recurrence was associated with 5-year survival rates of 9% to 11% and 10-year survival rates of 5%.[9] Surgical excision with complete regional lymph node dissection is the cornerstone of management, followed by adjuvant therapy with IFN alfa-2b, in which patients derive limited clinical benefits that are most substantial with high-dose IFN alfa (HDI).[10-13] Overall, these patients continue to experience a high risk of relapse and death despite the best available standard management approaches, and there continues to be an urgent need to improve the clinical outcome. Recent advances in the treatment of metastatic melanoma are destined to make real differences in the management of these

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patients; neoadjuvant and locoregional therapeutic approaches appear to be very promising in terms of improving the surgical outcome and the risk of relapse and mortality.

NEOADJUVANT TREATMENT OF POTENTIALLY RESECTABLE LOCOREGIONAL METASTASES OF CUTANEOUS MELANOMA

Neoadjuvant therapy has improved the outcome of patients with multiple different solid tumors, including head and neck, breast, bladder, esophageal, and rectal cancers.[14-17] Benefits include improvements in survival, surgical resectability, local control, and organ preservation. Other advantages of neoadjuvant therapy are the ability to evaluate the clinical and pathologic responses and the potential to identify immunologic and histologic correlates of tumor response. Access to tumor tissue before and after neoadjuvant therapy also may allow a better understanding of the antitumor mechanisms of action that may enable more selective application of therapeutic agents to those patients who are more likely to benefit. Such findings would improve the therapeutic index and cost-effectiveness of these agents. Neoadjuvant studies of chemotherapy, BCT, and immunotherapy have been investigated in melanoma, with several important findings. Table 1 provides a summary of these studies.

Neoadjuvant Chemotherapy and Biochemotherapy Studies in Patients with Melanoma with Locoegional Metastases

A phase II study tested neoadjuvant temozolomide (TMZ) in chemotherapy-naive patients who had melanoma with surgically resectable, locoregionally advanced disease.[18] Two cycles of 75 mg/m^2/day oral TMZ were given preoperatively for 6 weeks of every 8-week cycle. The response rate, which included one partial response and two complete responses, was

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KEY POINTS

- Patients with locoregionally advanced melanoma continue to experience a high risk of relapse and death despite the best available standard management approaches.
- Neoadjuvant biochemotherapy demonstrated high tumor response rates but was eventually abandoned after failure to deliver survival benefits in randomized trials of metastatic disease.
- Neoadjuvant immunotherapy with interferon alfa and ipilimumab have yielded several important clinical and mechanistic findings.
- In drug development, biomarker and mechanistic studies can be accelerated through neoadjuvant studies because of the access to biospecimens before and during therapy.
- Newer targeted and immunotherapeutic agents and combinations currently are being translated into the neoadjuvant setting at an accelerated pace and carry significant promise.

16%. Four patients had stable disease, and 12 experienced disease progression. Overall, the observed clinical activity with neoadjuvant TMZ was not different from what is known in metastatic melanoma.

Neoadjuvant BCT demonstrated high tumor response rates in phase II studies but eventually was abandoned because of the failure of BCT to deliver survival benefits in randomized trials of metastatic disease. A neoadjuvant phase II study of concurrent BCT was conducted in patients with resectable locoregional metastases of cutaneous melanoma (stage III; nodal, satellite/in-transit metastases and/or local recurrence).[19] In total, 65 patients were treated with two to four cycles of BCT before surgery, as summarized in Table 1. Two additional postoperative courses were given to patients who experienced tumor response after two preoperative courses. Among patients whose responses were assessed histologically, a partial response was reported in 27 patients (43.5%), and a pathologic complete remission (pCR) was reported in 6.5%; the overall response rate was 50%. Patients who experienced pCR had a significantly lower tumor burden (p = 0.02).[19] In a second phase II study that enrolled 48 patients, two cycles of BCT were administered before and after complete lymph node dissection using a BCT regimen similar to the prior study. Clinical responses were observed in 14 (38.9%) of 36 patients who had measurable disease; 13 (36.1%) experienced partial responses, and one patient (2.8%) experienced a complete response. A pCR was noted in four patients (11.1%). At a median follow-up of 31 months, 38 (79.2%) of the 48 patients were alive, and 31 patients (64.6%) remained free of disease progression.[20]

The phase II BCT studies indicated that neoadjuvant BCT is clinically active in patients who have melanoma with locoregional metastases. However, BCT has failed to demonstrate a survival advantage versus chemotherapy alone in phase III randomized trials in patients with stage IV disease.[21,22] Furthermore, chemotherapies as single agents or in combinations have not been shown to have a survival impact in patients with metastatic melanoma. IFN alfa and interleukin-2 (IL-2) used in the BCT regimens were administered at potentially suboptimal low dosages; also, in combination with chemotherapy, there is the potential for interactions of IFN alfa or IL-2 with chemotherapeutic agents, some of which have been shown to be immunosuppressive.[23] These factors may potentially antagonize or alter the immunotherapeutic effects of IFN alfa and IL-2. Of note, a phase III trial of adjuvant BCT in patients with high-risk, surgically resected melanoma (S0008) reported improved relapse-free survival but no difference in overall survival and more toxicity than HDI.[24]

Neoadjuvant Immunotherapy Studies

Several observations support the adjuvant and neoadjuvant evaluation of immunotherapeutic agents in patients with surgically resectable melanoma at high risk for death as a result of melanoma recurrence. Host immune resistance of melanoma plays a key role in disease control in the adjuvant and advanced disease settings and appears to have important implications for neoadjuvant immunotherapy of patients

TABLE 1. Neoadjuvant Studies of Resectable Locoegional Metastases of Cutaneous Melanoma

Study	No. of Patients	Design	Primary Objective	Regimen	Important Findings
Buzaid et al[19]	64	Phase II single arm	Tumor response	2-4 (3-week) cycles; days 1-4: 20 mg/m^2 IV cisplatin, 1.5 mg/m^2 IV vinblastine, 9 MIU/m^2/d continuous IV IL-2; day 1 only: 800 mg/m^2 IV dacarbazine; days 1-5: 5 MU/m^2 SC IFN alfa-2a	High tumor response rates in phase II studies but eventually abandoned, with the failure of biochemotherapy to deliver survival benefits in randomized trials of metastatic disease
Gibbs et al[20]	48	Phase II single arm	Tumor response	2 (3-week) cycles; days 1-4: 20 mg/m^2 IV cisplatin, 1.6 mg/m^2 IV vinblastine, 9 MIU/m^2/d continuous IV IL-2; day 1 only: 800 mg/m^2 IV dacarbazine; days 1-5: 5 MU/m^2 SC IFN alfa-2a	
Shah et al[18]	19	Phase II single arm	Tumor response	2 (8-week) cycles 75 mg/m^2/d temozolomide for 6 weeks then 2 weeks off	The observed clinical activity was not different from what is known in metastatic melanoma
Moschos et al[30]	20	Phase II single arm	Tumor response	20 MU/m^2 IV IFN alfa-2b 5 days a week for 4 weeks before surgery (induction) / 20 MU/m^2 SC IFN alfa-2b 3 days a week for 48 weeks starting after surgery (maintenance)	Promising clinical activity. HDI upregulated pSTAT1 and TAP2 and downregulated pSTAT3. Significant increases in endotumoral CD11c$^+$ and CD3$^+$ cells were noted after HDI. Phospho-ERK1/2 was downregulated by HDI in tumor cells but not in lymphocytes
Tarhini et al[35]	33	Phase I/II single arm	Safety, biomarker	10 mg/kg IV ipilimumab every 3 weeks for 2 doses, bracketing surgery	Promising clinical activity. Ipilimumab led to potentiation of type I CD4 and CD8 tumor-specific T cells, downregulation of MDSC, and an increase of CD8$^+$ TIL and T-cell memory (CD45RO$^+$). An immune-related gene expression signature was significantly associated with clinical benefit

Abbreviations: IV, intravenously; IL, interleukin; SC, subcutaneously; IFN, interferon; HDI, high-dose IFN alfa; MDSC, myeloid-derived suppressor cells; TIL, tumor-infiltrating lymphocytes.

with high-risk, locoregionally advanced disease.[5,10] Spontaneous regression has been reported in melanoma, which suggests a role for host immunity that is indirectly supported by the presence of lymphoid infiltrates at primary melanoma sites associated with tumor regression.[25] Host cellular immune response within melanoma has potential disease prognostic and immunotherapeutic predictive significance. T-cell infiltrates are prognostic of disease outcome in primary melanoma and in melanoma that is metastatic to regional nodes.[25-28] Furthermore, T-cell infiltrates within regional nodal metastasis are significantly associated with benefit from neoadjuvant IFN alfa therapy.[26,29,30] Further, evidence supports a difference in the quality of the host immune response of patients with earlier (operable) and more advanced (inoperable) melanoma. Although T-helper type 1 (Th1)–type CD4$^+$ antitumor T-cell function appears critical to the induction and maintenance of antitumor cytotoxic T-lymphocyte responses in vivo, and although Th2- or Th3/T regulatory-type CD4$^+$ T-cell responses may subvert Th1-type cell-mediated immunity and provide a microenvironment conducive to disease progression, patients with advanced melanoma or renal cell carcinoma have displayed strong tumor antigen-specific Th2-type polarization. Conversely, normal donors and patients who were disease free after therapy demonstrated either a weak mixed Th1-/Th2-type or a strongly polarized Th1-type response to the same epitopes.[31] Therefore, factors of host immune tolerance that seem to impede immunotherapeutic benefits in advanced disease may be less pronounced in the high-risk, operable setting. In patients with earlier-stage melanoma, the host may be more susceptible to immunologic interventions that may potentiate an antitumor T-cell response and create lasting immunity.

Neoadjuvant HDI was investigated in patients who had melanoma with palpable regional lymph node metastases presenting either with clinical AJCC stage IIIB to IIIC disease (TanyN2b,2c,3) or with recurrent regional lymphadenopathy. Patients underwent surgical biopsy at study entry and then received standard intravenous HDI (20 million units/m^2 on 5 days per week) for 4 weeks followed by complete lymphadenectomy and standard maintenance subcutaneous HDI (10 million units/m^2 3 times per week) for 48 weeks. Biopsy samples were obtained before and after intravenous HDI. Twenty patients were enrolled, and biopsy samples were informative for 17. Eleven patients (55%) demonstrated a clinical response, and three patients (15%) had a pCR. At a median follow-up of 18.5 months, 10 patients had no evidence of recurrent disease. By comparison, in the setting of inoperable metastatic disease, response rates of less than 20% were reported, although a number of patients had durable responses that ranged from 26 months to more than 30 months.[32] In the context of this neoadjuvant study, HDI was found to upregulate pSTAT1, whereas it downregulates pSTAT3 and total STAT3 levels in both tumor cells and lymphocytes. Higher pSTAT1/pSTAT3 ratios in tumor cells before treatment were associated with longer overall survival ($p = 0.032$). The pSTAT1/pSTAT3 ratios were augmented by HDI both in melanoma cells ($p = 0.005$) and in lymphocytes ($p = 0.022$). Of the immunologic mediators and markers tested, TAP2 (but not TAP1 and major histocompatibility complex [MHC] classes I/II) was augmented by HDI.[33] In

addition, HDI regulated mitogen-activated protein kinase (MAPK) signaling differentially in melanoma tumor cells and host lymphoid cells. HDI significantly downregulated pSTAT3 (p = 0.008) and phospho-MEK1/2 (p = 0.008) levels in tumor cells. Phospho-ERK1/2 was downregulated by HDI in tumor cells (p = 0.015) but not in lymphoid cells. HDI downregulated epidermal growth factor receptor (EGFR; p = 0.013), but pSTAT3 activation did not appear associated with EGFR expression and the MEK/ERK MAPK pathway, which indicates that STAT3 activation is independent of the EGFR/MEK/ERK signaling pathway.[34] Clinical responders had significantly greater increases in endotumoral CD11c+ and CD3+ cells and significantly greater decreases in endotumoral CD83+ cells than nonresponders.[30]

Neoadjuvant ipilimumab was tested in locoregionally advanced melanoma to evaluate safety and to define markers of activity and toxicity in the blood and tumor of patients at baseline and early on-treatment times.[35] Patients were treated with ipilimumab (10 mg/kg intravenously every 3 weeks for two doses) that bracketed surgery. Tumor and blood samples were obtained at baseline and at the definitive surgery time. Thirty-five patients were enrolled; diseases were stages IIIB (three patients; N2b), IIIC (32 patients; N2c, N3), and IV (two patients). The worst toxicities included grade 3 diarrhea/colitis (five patients; 14%), hepatitis (two patients; 6%), rash (one patient; 3%), and elevated lipase (three patients; 9%). The median follow-up was 19 months. Among 33 evaluable patients, the preoperative radiologic assessment by PET-CT scans at 6 to 8 weeks after the initiation of ipilimumab revealed that three patients (9%) had objective responses (two patients, complete response; one patient, partial response). Twenty-one patients (64%) had stable disease, and eight patients (24%) experienced disease progression identified with PET-CT. [18F]-fludeoxyglucose PET/CT parameters at baseline (T0) and at the first scan after two doses of ipilimumab (T1) were unable to predict recurrence after surgery (at a significance level of 0.05).[36] The number of lesions at T1 showed a trend toward predicting a higher chance of disease recurrence (p = 0.06). The median recurrence-free survival was 11 months (95% CI, 6.2 to 19.2 months). The probability of 12-month overall survival was 96%. Based on preliminary data from a study that tested HDI and tremelimumab in patients with metastatic disease and on recent data in the literature, we evaluated candidate biomarkers linked to the proinflammatory immune response and markers of immunosuppression as assessed in the tumor microenvironment (TME) and in circulation that may have therapeutic predictive roles in relation to immunotherapy for melanoma.[37] The underlying hypothesis was that our quest for a predictive biomarker signature in patients with metastatic melanoma who are treated with immunotherapy may be rewarded by evaluating candidate biomarkers in the TME and in circulation simultaneously, on the basis of the common systems of biology.[38]

Neoadjuvant ipilimumab leads to a significant potentiation of type I CD4 and CD8 tumor-specific T cells that may play a therapeutic predictive role.[35] Here, multicolor flow cytometry that used overlapping peptide pools (gp-100, MART-1, NY-ESO-1) showed baseline evidence of spontaneous in vivo cross-presentation that resulted in type I CD4+ and CD8+ antigen-specific T-cell immunity.[35] Ipilimumab induced a significant increase in type I CD4 and CD8 (fully activated and IFN gamma–producing) antigen-specific T cells. Both CD4+ and CD8+ T cells were activated (upregulated CD69) on their stimulation with individual antigen peptide pools, and a subset secreted IFN gamma. High increases (3- to 10-fold) in CD3+/CD4+/IFN gamma+ T cells were seen only in patients who were progression free at 6 months, which suggests a potential early on-treatment therapeutic predictive value. A significant modulation of circulating regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC) also was seen. A significant increase in the frequency of circulating Treg (CD4+/CD25hi+/Foxp3+ [p = 0.02] and CD4+/CD25hi+/CD39+ [p = 0.001]) from baseline to 6 weeks was observed. Significant decreases in circulating MDSC were seen. A decrease in the circulating monocyte gate MDSC Lin1-/HLA-DR-/CD33+/CD11b+ was associated with improved progression-free survival (PFS; p = 0.03). Increases in Treg were associated with improved PFS (hazard ratio = 0.57; p = 0.034). In the tumor, Treg (CD4+/CD25hi+, CD4+/CD25hi+/Foxp3+) appeared higher at week 6 in the progressive-disease group but the opposite occurred in the disease control group (p = 0.09). Tumor samples obtained at baseline and after ipilimumab were tested by immunohistochemistry and showed significant increases in CD8+ tumor-infiltrating lymphocytes after ipilimumab (p = 0.02). By flow, trends were observed in examination of the change in Treg and disease control (p = 0.09). Treg were higher at week 6 in the progressive-disease group, whereas the opposite was seen in the disease control group. This was unlike what we observed in the circulation. Ipilimumab also induced T-cell activation, as evidenced by CD69 without in vitro stimulation. There was evidence of induction/potentiation of T-cell memory (CD45RO+) but not naive status (CD45RO-) in the tumor, which also supported further testing as a predictive marker, as suggested from data by Galon et al in colorectal tumors.[39] Gene expression profiling was performed on the tumor biopsies and identified immune-related genes that were significantly differentially expressed on the basis of clinical outcome. A baseline gene signature that resulted from this analysis was significantly associated with clinical benefit of neoadjuvant ipilimumab.[40] These data have laid the groundwork for a series of subsequent studies that are evaluating potentially therapeutically predictive biomarkers of a proinflammatory immune response and of immunosuppression both in the TME and in circulating blood in patients with melanoma who are receiving immunotherapy.

Neoadjuvant Efforts Using Molecularly Targeted Agents

Driver oncogenic mutations identified in melanoma have defined clinically relevant melanoma molecular subsets that can be targeted therapeutically, leading to giant leaps in metastatic melanoma management.[41,42] Significant clinical activ-

ity in early studies of *BRAF* and MEK kinase inhibitors led to a rapid succession of phase II and III studies completed at an unprecedented pace, which prompted the regulatory approval of at least three targeted agents (i.e., vemurafenib, dabrafenib, and trametinib).[43,44] Anecdotal experiences with neoadjuvant vemurafenib and dabrafenib have been reported, and evaluations are underway in a number of clinical trials.[45,46]

FUTURE DIRECTIONS IN THE NEOADJUVANT THERAPY OF MELANOMA

Neoadjuvant therapy ideally would be applied in patients with locally advanced melanoma for whom immediate surgery is not feasible, with the goal of allowing definitive surgical resection and improvement in local and regional disease control. In these high-risk patients, neoadjuvant therapy also may target distant micrometastases that may be the source of postoperative distant relapse if systemic therapy was delayed because of surgery or complications related to surgery. Neoadjuvant therapy has improved survival in patients with multiple malignancies, including breast, bladder, cervical, and esophageal cancers.[15,17] Similarly, the rapidly expanding number of effective therapeutic agents and regimens in metastatic melanoma allow for these new agents to be evaluated in the neoadjuvant setting, where significant improvements in clinical outcome are expected. Further, in providing access to biospecimens before and after therapy, such studies are likely to provide significant mechanistic insights and biomarker findings that may have important and lasting impacts on the field of cancer.

Molecularly Targeted Combinations

Initial response rates of approximately 50%, lasting a median of 6 to 7 months, with *BRAF* inhibitor monotherapy were significantly improved to approximately 60% to 70%, and a median duration of response of approximately 9 months, with the combination of *BRAF* and MEK inhibitors.[6,42,43] Overall, *BRAF* and MEK inhibitors have been validated as effective therapies for *BRAF*-mutant metastatic melanoma. This high and unprecedented response rate with *BRAF*/MEK inhibitor therapy makes this regimen an ideal cytotoxic regimen that may improve the operability of locally advanced disease. Relevant to this hypothesis, several studies are ongoing. However, resistance ultimately develops in the majority of patients with metastatic disease, and several resistance mechanisms have been well characterized.[47] Future studies optimizing MAPK pathway inhibition (targeting ERK and CDK4/6 as monotherapy and in combinations) and combinations that target alternate pathways implicated in mediating resistance (e.g., phosphoinositide 3-kinase [PI3K] and AKT), may take advantage of the neoadjuvant approach. Combination studies with immunotherapy (including IFN, IL-2, anti-CTLA4, and anti–PD-1/PD-1 ligand [PDL-1]) that are underway in patients with metastatic disease also may be transitioned into the neoadjuvant setting, supported by the hypothesis that the high response rates seen with *BRAF*/MEK

inhibitors can be transformed into high durable response rates with immunotherapy.[48] Among ongoing targeted neoadjuvant combination studies are trials with vemurafenib/cobimetinib (NCT02303951, NCT02036086) and dabrafenib/trametinib (NCT01972347, NCT02231775).

Intralesional Immunotherapy As Neoadjuvant Therapy

Intralesional therapy of melanoma has consisted of immunotherapeutic approaches that involve cytokines, bacterial extracts, and genetically engineered viral agents. The goals of therapy consist of local tumor regression in injected metastases and induction of systemic immune responses that may affect distant noninjected tumors. Several studies tested intralesional bacillus Calmette-Guérin with promising early reports of local and distant disease control.[49,50] However, these early findings with intralesional therapy were not reproduced in later adjuvant studies, which led to a halt in development.[51] Intralesional injection of granulocyte-macrophage colony-stimulating factor (GM-CSF), IFN alfa, or IFN beta also were tested, and modest clinical activity was found.[52-54] Promising results were reported with intralesional rose bengal (PV-10).[55] A phase II study in stage III/IV melanoma reported an overall response rate of 51%. Responses were seen in both injected and bystander tumor lesions. A phase II study of coxsackievirus A21 in stage IIIC/IV melanoma reported an immune-related PFS at 6 months of 35% and a response rate (by immune-related RECIST 1.1 criteria) of 24%.[56] An intralesional approach involving plasmids coding for the HLA B7 antigen (allovectin-7) showed encouraging early results but did not meet phase III testing endpoints.[57] Talimogene laherparepvec (T-VEC) is an oncolytic immunotherapy comprising a herpes simplex virus type 1 backbone with the gene for GM-CSF. Promising early studies led to a phase III trial that tested intralesional therapy with T-VEC versus GM-CSF in stage IIIB/IV melanoma.[58] Durable and overall response rates with T-VEC were 16.3% and 26.4%, respectively. The median survival times for the study population were 23.3 months with T-VEC versus 18.9 months with GM-CSF (p = 0.051).[58] Overall, intralesional approaches have been relatively safe and well tolerated, with evidence of local and bystander/distant antitumor clinical activity that appears to be most promising with T-VEC at this time. This approach may provide a neoadjuvant therapeutic platform that can be combined with other immune-activating agents, including cytokines and checkpoint inhibitors. Combination studies of T-VEC with anti-CTLA4 and anti–PD-1 antibodies are underway in metastatic disease, and at least one neoadjuvant study with T-VEC monotherapy is planned in resectable regionally advanced melanoma (NCT02211131).

Evaluation of Newer Immune Checkpoint Inhibitors and Combinations

In a recent analysis of 1,861 patients with melanoma who were treated with ipilimumab in clinical trials, 22% were still alive at 3 years, where survival plateaued at a maximum follow-up of approximately 10 years.[59] These data illustrate the potential for cure with ipilimumab that may be more significant in patients

with earlier disease stages treated in the adjuvant and neoadjuvant settings.[31] Targeting PD-1 and PDL-1 in clinical trials has demonstrated early results of significant clinical activity, which has led to the regulatory approval of two potent and highly selective humanized monoclonal antibodies: pembrolizumab and nivolumab.[59,60] These agents have shown an unprecedented rate of durable tumor responses, exceeding 20% to 30% with single-agent immunotherapy.

Efforts in combination immunotherapy have already demonstrated significant results with the combination of ipilimumab and either nivolumab, GM-CSF, bevacizumab, or IL-2 and the combination of IFN alfa and tremelimumab; these efforts have led to subsequent randomized trials.[37,62-65] An impressive 2-year survival rate of 79% was reported recently in an update of the nivolumab/ipilimumab phase I combination trial.[66] Several other combination studies are underway that take advantage of nonredundant immune activation and T-cell differentiation mechanisms. Studies of novel immune checkpoint modulators targeting CD40, OX40, CD137, TIM3, and LAG3, among others, also are ongoing.[67] In addition, combination studies testing checkpoint inhibitors and other proinflammatory cytokines (IL-12, IL-15) are in the planning phases. These agents and combinations currently are being translated into the neoadjuvant setting; ongoing studies involve the combinations of ipilimumab and HDI (NCT01608594) and pembrolizumab and HDI (NCT02339324).

Biomarkers Predictive of Therapeutic Benefit

Aside from targeted therapy for *BRAF*-mutant melanoma, the current paradigm of systemic therapy of metastatic melanoma involves the nonselective treatment of patients with immunotherapy, despite evidence showing that only a proportion will derive significant benefits. Therefore, there is a need for predictive biomarkers that are selected on the basis of their capacity to classify patients according to the degree of benefit from treatment or the risk for significant toxicity.

Neoadjuvant studies that allow access to blood and tumor biospecimens before and after the initiation of systemic therapy provide an ideal platform for investigating such biomarkers that, ideally, can be evaluated simultaneously in the circulation and in the TME according to the common systems of biology.[35] Significant efforts in melanoma biomarker studies are underway, and preliminary data—including gene expression signatures reflective of an inflamed TME that may predict clinical benefit in patients treated with ipilimumab, tumor vaccines, and IL-2—are very promising.[35,40,69] Similarly, exome sequencing studies have elucidated a neoantigen landscape specific for tumors that respond to CTLA-4 blockade.[70] Further, immunohistochemistry studies of CD8 expression at the tumor invasive margin support the predictive value of this biomarker in relation to anti-PD1 therapeutic benefit.[71] Similar efforts are underway that may allow the prediction of patients who are more likely to experience severe immune-related toxicities. Such biomarker and mechanistic studies can be accelerated through neoadjuvant studies, given the access to biospecimens.

CONCLUSION

Neoadjuvant therapy has the potential to improve the outcomes—including survival, surgical resectability, local control, and organ preservation— of patients with locoregionally advanced melanoma. Other advantages are the ability to evaluate the clinical and pathologic responses and the potential to identify immunologic and histologic correlates of tumor response. Access to tumor tissue before and after neoadjuvant therapy may allow a better understanding of the antitumor mechanisms of action that may enable more selective application of therapeutic agents to those patients who are more likely to benefit. Neoadjuvant immunotherapy with HDI and ipilimumab has yielded several important findings, and multiple studies involving newer immunotherapeutic and targeted agents and combinations are underway. Neoadjuvant therapy in melanoma continues to be investigational and should only be pursued in the context of a clinical trial.

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Targeted Molecular Therapy in Melanoma

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Achievements and Challenges of Molecular Targeted Therapy in Melanoma

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OVERVIEW

The treatment of melanoma has been revolutionized over the past decade with the development of effective molecular and immune targeted therapies. The great majority of patients with melanoma have mutations in oncogenes that predominantly drive signaling through the mitogen activated protein kinase (MAPK) pathway. Analytic tools have been developed that can effectively stratify patients into molecular subsets based on the identification of mutations in oncogenes and/or tumor suppressor genes that drive the MAPK pathway. At the same time, potent and selective inhibitors of mediators of the MAPK pathway such as RAF, MEK, and ERK have become available. The most dramatic example is the development of single-agent inhibitors of BRAF (vemurafenib, dabrafenib, encorafenib) and MEK (trametinib, cobimetinib, binimetinib) for patients with metastatic BRAF^{V600}-mutant melanoma, a subset that represents 40% to 50% of patients with metastatic melanoma. More recently, the elucidation of mechanisms underlying resistance to single-agent BRAF inhibitor therapy led to a second generation of trials that demonstrated the superiority of BRAF inhibitor/MEK inhibitor combinations (dabrafenib/trametinib; vemurafenib/cobimetinib) compared to single-agent BRAF inhibitors. Moving beyond BRAF^{V600} targeting, a number of other molecular subsets—such as mutations in *MEK*, *NRAS*, and *non-V600 BRAF* and loss of function of the tumor suppressor neurofibromatosis 1 (*NF1*)—are predicted to respond to MAPK pathway targeting by single-agent pan-RAF, MEK, or ERK inhibitors. As these strategies are being tested in clinical trials, preclinical and early clinical trial data are now emerging about which combinatorial approaches might be best for these patients.

Traditionally, melanoma has been a challenging disease to treat because chemotherapy is typically not effective and cytokine therapy, such as high-dose interleukin-2 (HD IL-2), only helps a small percentage of patients.[1] Highlighting the futility of early approaches to the development of effective therapies for melanoma, from 1976 to 2011 the U.S. Food and Drug Administration (FDA) approved only dacarbazine and HD IL-2 for the treatment of metastatic melanoma, and neither agent was demonstrated to be associated with an overall survival advantage. Over the past decade, however, great advances in immune-targeted and molecular-targeted therapies have led to a therapeutic revolution. Since 2011, six agents, including three immunotherapies (ipilimumab, pembrolizumab, nivolumab) and three molecular targeted therapies (vemurafenib, dabrafenib, trametinib), have received regulatory approval.[2] The following section summarizes genomic approaches for molecular subtyping, outlines the rationale for molecular targeted therapy in melanoma, and reviews the successes and challenges of this strategy.

Melanoma is a malignancy that arises from melanocytes, the pigment producing cells in the body that may be derived from a number of different anatomic sites including skin, mucosal surfaces, conjunctiva, and uveal structures. With the

emergence of powerful molecular diagnostic tools, a number of genetic mutations and amplifications/deletions have been identified that appear to drive tumor growth and survival signaling and render these cells sensitive to small-molecule inhibitors.[3] The great majority of these genetic aberrations lead to constitutive activation of the MAPK pathway (Fig. 1A).[4] Mutations in the serine-threonine kinase *BRAF*, particularly at the 600 position with substitution of valine with either glutamate (V600E) or lysine (V600K), drive signaling though the MAPK pathway and are present in more than 50% of patients with cutaneous melanoma, 10% to 20% of melanomas arising in mucosal or acral locations, and 0% of uveal melanomas.[5-7] Mutations upstream of BRAF, in particular activating *NRAS* mutations and loss-of-function mutations of neurofibromatosis 1 (*NF1*, a major regulator of NRAS activation), are the MAPK pathway drivers in nearly 30% of melanomas and are typically mutually exclusive of *BRAF^{V600}* mutations.[3,8,9] Interestingly, 20% to 30% of mucosal melanomas harbor either a mutation or genomic amplification of *CKIT*, which is rarely aberrant in cutaneous melanoma, and more than 80% of uveal melanomas contain a mutation in one of two G-protein subunits, *GNAQ* and *GNA11*, also rarely seen in cutaneous melanoma.[10-13] Both *CKIT* and *GNAQ/GNA11*

FIGURE 1. Relevant Signaling Cascades in Melanoma
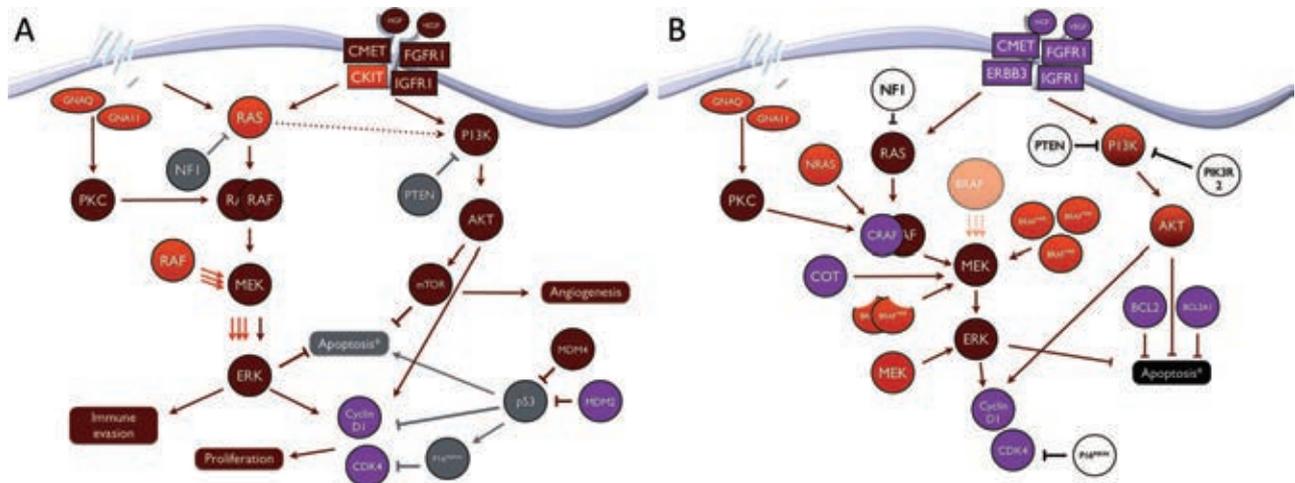
Multiple mediators and regulators of the MAPK and PI3K pathways have been linked to melanoma. (A) Key oncogenic mutations (red), amplifications (purple), and tumor suppressor genes (gray). (B) Genetic aberrations that mediate resistance to treatment with BRAF inhibitors (driving mutation, red; genomic amplification, purple; and loss of tumor suppressor, gray).

aberrations lead to MAPK signaling.[11,12,14-16] Recently, a number of small-molecule inhibitors have been developed that inhibit many of the key mediators of the MAPK pathway including RAF (pan-RAF and BRAF-specific), MEK, and ERK, as well as upstream activators of the pathway such as CKIT.

GENOMIC APPROACHES TO MOLECULAR DIAGNOSIS AND TARGET DISCOVERY

Early in the development of potent and specific BRAF inhibitors it became clear that only patients with *BRAF* mutations

KEY POINTS

- The great majority of patients with melanoma have mutations in genes (oncogenes and/or tumor suppressor genes) that drive MAPK pathway activation.
- Potent and specific inhibitors of MAPK pathway mediators have been discovered and include BRAF inhibitors (vemurafenib, dabrafenib, encorafenib), MEK inhibitors (trametinib, selumetinib, cobimetinib, binimetinib), ERK inhibitors (BVD-523, GDC-0994), and pan-RAF inhibitors (LY3009120).
- Combination BRAF/MEK inhibition is superior to single-agent BRAF inhibition in patients with *BRAF^V600*-mutant melanoma; a number of trials of BRAF/MEK inhibition plus a third targeted agent are underway to determine whether triplet therapy is superior to BRAF/MEK doublet therapy.
- Single-agent pan-RAF, MEK, and ERK inhibitor therapies may be effective strategies for the treatment of other molecular subsets of melanoma, including uveal melanoma (typically either *GNAQ* or *GNA11* mutant), *NRAS*-mutant, *MEK*-mutant, non-V600 *BRAF* mutant, and *NF-1* loss of function.
- The use of novel molecular targeted therapies, alone or in combination, holds great promise for the treatment of melanoma, but is not without challenges.

were benefiting from these therapies. As a result, both Roche-Genentech and GlaxoSmithKline (GSK) developed companion diagnostics that were used to prescreen patients for the pivotal trials of vemurafenib and dabrafenib, respectively. Whereas the first generation of mutation detection analytics used direct sequencing, both the Roche assay (known as the cobas 4800 BRAF V600 Mutation Test) and the assay developed by GSK (THxID-BRAF test, licensed by Quest Diagnostics and bioMerieux) involve polymerase chain reaction (PCR) techniques—real-time PCR for the cobas assay and amplification refractory mutation system (ARMS)-PCR for the THxID-BRAF assay— using primers designed to quantify predominantly V600E (cobas) or both V600E and V600K (THxID-BRAF).[17,18] Both assays have been shown to be superior to Sanger sequencing, although the cobas assay only detects 70% of V600K mutations whereas the THxID-BRAF test is able to detect these with great accuracy, and both received FDA approval concurrently with vemurafenib (cobas) and dabrafenib (THxID-BRAF).[17-19] However, as described above, a number of additional mutations have been identified that might similarly be targeted with small-molecule inhibitors, including non-V600 *BRAF*, *NRAS*, *CKIT*, and *NF1* loss; thus molecular analysis platforms that can accurately and cost-effectively analyze multiple mutations are required.

A number of novel techniques to target mutant epitopes across relevant genes have been developed, including those that use mass spectrometry (Sequenom) and florescent tags (SNaPshot), but these are now being replaced by massively parallel sequencing techniques that can detect single nucleotide variants, insertions, deletions, and gene rearrangements with deep coverage.[20-22] As these assays become more widely available, the challenge for providers will be to determine how best to utilize the vast amount of information. It is expected that these types of effort will identify small subsets of patients with novel genetic aberrations that predict response to agents not previously used in melanoma.

BRAF^V600 TARGETING, RESISTANCE, AND OVERCOMING RESISTANCE

With the original observation that oncogenic mutations in BRAF were present and driving tumor growth in more than 65% of melanomas (although later the prevalence was determined to be closer to 50%), efforts to therapeutically target BRAF were undertaken.[3,5] Although the initial focus was on small molecules that blocked a wide range of kinases including RAF (sorafenib, RAF265), eventually more potent and specific inhibitors that preferentially targeted mutant isoforms of RAF (particularly at the 600 position) were tested in the clinic and have revolutionized the treatment of BRAF-mutant melanoma.[23-27] Both vemurafenib and dabrafenib were determined to be superior to chemotherapy in phase III trials, as was the MEK1/2 inhibitor trametinib, although unfortunately disease progression typically occurred within 5 to 7 months with single-agent BRAF and MEK inhibitors.[28-30] More recent strategies have demonstrated the safety of combined BRAF/MEK targeting (dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib), as well as the superiority of the combination with respect to response rate, progression-free survival (PFS), and overall survival (OS) in three randomized trials (COMBI-d, COMBI-v, co-BRIM).[31-36] Unfortunately, innate (primary) and acquired (secondary) resistance remain central obstacles to optimal BRAF-targeting therapy (Fig. 1B).

Tumor Heterogeneity and Innate Resistance

Melanoma primary tumors and metastases are highly heterogeneous with regard to their genomic, epigenomic, and transcriptional profiles. This heterogeneity is hard to explain by the cancer stem cell model. Moreover, many studies suggest that melanomas are not hierarchically organized, but suggest an extraordinary plasticity in several tumor subpopulations that are supported by the microenvironment. Slow-cycling tumor cell populations (such as JARID1B-positive melanoma cells) and tumor cells with an epithelial mesenchymal transition (EMT)-like phenotype (i.e., an invasive mesenchymal phenotype) contribute significantly to tumor maintenance and growth. This plasticity may facilitate a nonhierarchical organization of the tumor that supports adaptation and survival during a major stress situation as the sudden interruption of MAPK signaling.[37] This may explain why BRAF inhibitors cause only limited cell death in vitro and in vivo during targeted therapy. Pretreatment overexpression of antiapoptotic BCL2 family members, namely BCL2 and BCL2A1, has also been associated with resistance to BRAF inhibitors and may be an alternative explanation for the limited apoptosis associated with BRAF inhibitors.[38,39] Other mechanisms of primary resistance include genetic aberrations that lead to cell cycle activation (including cyclin D amplification/expression, p16 loss, and CDK4 activation) or parallel growth factor signaling (PTEN loss).[40-42]

Tumor Heterogeneity and Acquired Resistance

Even after an impressive clinical response, most patients experience progression of disease after months, and sometimes years, of successful tumor control by mono- or combination therapy with single-agent BRAF and/or MEK kinase inhibitors. The range of response duration is quite broad, ranging from weeks to years, and the resistance mechanisms causing the treatment failure have been the subject of intense scientific scrutiny. Based on high-throughput analysis of transcriptional profiles of many primary melanoma cell cultures from different laboratories worldwide, the phenotype-switching model was established.[43] In this context, the transcriptional adaptation induced by interruption of the MAPK pathway by RAF or MEK kinase inhibitors can be interpreted as a shift from the proliferative to the invasive (stem-like, EMT-like) phenotype associated with reduced glucose metabolism.[44] In doing so, melanoma cells will gain time to acquire resistance by the activation of alternative signaling pathways, such as through the selection of tumor cells with additional activating mutations.

Detailed analyses of biopsies before therapy, during tumor regression, and during relapse have provided evidence that adaptive mechanisms, as shown by elevated ERK1/2 phosphorylation levels in progressive lesions, and genomic alterations, such as activating mutations in MEK and NRAS, contribute to reactivation of the MAPK pathway.[45] The first report on this phenomenon described a de novo MEK1 mutation (P124L) in a regrowing metastasis in a patient with BRAF-mutated cancer that was successfully treated with the MEK inhibitor selumetinib.[46] This MEK1 mutation conferred strong resistance to MEK inhibitors and mild resistance to the BRAF inhibitor vemurafenib. Although less frequent, the appearance of a MEK mutation that results in resistance against both BRAF and MEK inhibitors has also been reported.[47] Several investigations have identified concomitant NRAS mutations with the persistence of V600E BRAF.[47-49] This finding is of special interest because BRAF inhibitors may cause paradoxical pathway activation in this molecular context, as demonstrated for cutaneous epithelial malignancies associated with BRAF inhibitors.[50,51] Many of these issues are reflected by the results of deep exome sequencing approaches that compare the genetic landscape before and after targeted therapy.[47] In our understanding, the presence of an NRAS mutation at the time of progression is important because, if it is active, treatment beyond progression might result in a detrimental effect as a result of paradoxical activation of the pathway.

To date, so-called gatekeeper mutations in the kinase domain of BRAF have not been identified; however, BRAF amplification and truncated BRAF variants have been reported to mediate resistance to BRAF inhibitor therapy. Initially, BRAF amplifications were preferentially seen in BRAF-mutated melanoma cell cultures.[52] However, a comparison of pre- and post-treatment biopsies by deep exome sequencing demonstrated that BRAF amplification is associated with progressive disease.[53] Additionally, alterations in BRAF splicing result in a truncated BRAF protein that lacks exons 4 to 8, a region that encompasses the RAS-binding domain and contributes to resistance to BRAF inhibitors through enhanced protein dimerization and activation of the pathway.[54]

Resistance to BRAF inhibitors also has been described to occur through upregulation of parallel signaling pathways, such as the phosphoinoside-3-kinase (PI3K) pathway, or the MAPK pathway itself through alternative kinase activation.[55-57] One example of this latter scenario is resistance mediated through activation of the kinase COT.[58] Bypass signaling can also be facilitated by the tumor microenvironment. Cells derived from the stroma of resistant tumors secrete a number of growth and viability factors that are able to rescue melanoma cells from BRAF inhibition. Among them, hepatocyte growth factor (HGF) appears to a secreted factor that is able to sustain tumor cell growth via activation of the HGF receptor MET in a paracrine manner, leading to tumor upregulation of the PI3K pathway.[59,60] Interestingly, simultaneous amplification of HGF and MET, which suggests an autocrine activation loop, was detected in melanomas with rapid progression during MEK inhibition (Reinhard Dummer, MD, unpublished data, November 2014). Other growth factor receptors can also maintain proliferation during BRAF inhibition. For example, epidermal growth factor receptor (EGFR) is expressed by melanoma cells although the expression level is quite low compared to that in colon or squamous cell carcinomas. In cases of innate or acquired resistance, melanoma cells are able to secrete EGF and activate EGFR by an autocrine loop.[61,62] These observations are convincing examples of how the microenvironment and the secretome of stromal and tumor cells cooperate to create resistance.

Reports that allow to us to link various biochemical mechanisms such as maintenance of an eIF4F complex that is associated with reactivation of MAPK signaling, persistent ERK-independent phosphorylation of the inhibitory eIF4E-binding protein 4EBP1, or increased proapoptotic BCL-2–modifying factor (BMF)-dependent degradation of eIF4G are of special interest because they open new avenues for intervention.[63] Recently, secretion of interferon beta was found to be associated with BRAF inhibition and tumor regression. In cases of resistance, PKCε-phosphorylated ATF2 downregulates interferon beta-1 expression (and signaling), which promotes the resistance of melanoma cells to chemotherapeutic agents.[64]

Strategies to Overcome Resistance

Today, the combination of BRAF and MEK inhibitors is the backbone of targeted therapy in BRAF-mutated melanoma. Depending on resistance mechanisms present in the individual patient, the addition of a third inhibitor might overcome resistance. Candidates for third agents in "triplet regimens" include a cyclin-dependent kinase inhibitor, an receptor tyrosine kinase (RTK) inhibitor (including MET, fibroblast growth factor receptor, or vascular endothelial growth factor inhibitor), an inhibitor targeting a key mediator of a parallel growth factor pathway (e.g., PI3K, AKT, mTOR inhibitors), or an agent targeting apoptosis.[65,66] A major challenge in this context is how reliably the principal mechanism of resistance can be identified in one individual and whether this mechanism is relevant for all metastases in a given patient. In addition, there

could be safety issues as the simultaneous delivery of multiple drugs might be associated with intolerable toxicity.

Moving forward, the integration of antibody therapy with targeted therapy also holds promise for overcoming resistance to current targeted therapy regimens.[67] For example, resistance to BRAF inhibition has been associated with increased MAPK signaling as well as increased expression of programmed death-ligand 1 (PD-L1), enabling melanoma cells to avoid destruction through immune suppression.[68] The combination of immunotherapy against PD-L1 with inhibitors of MAP kinase pathway targets downstream of BRAF, such as MEK, represents a promising novel strategy for overcoming such resistance and improving patient outcomes.[67-69]

Another possible approach to overcome resistance is intermittent therapy with drug holidays. In a xenograft model of primary human melanoma the proliferation of vemurafenib-resistant melanomas became drug dependent, implying that interruption of drug administration could cause regression of established drug-resistant tumors. As a consequence, intermittent dosing delayed resistance to vemurafenib.[70] It remains to be seen whether this observation is relevant for combination kinase inhibitor therapy. This strategy needs to be investigated as an approach to cope with resistance in carefully designed clinical trials.

TARGETING ANYTHING BUT BRAF

As described above, the landscape of mutations, deletions, and amplifications identified in patients with metastatic melanoma has been analyzed as part of The Cancer Genome Atlas. Although the functional significance of each specific mutation has not been determined, there are a number of relatively common mutations that appear to be critical drivers of oncogenic signaling and may be targetable (either directly or indirectly) with small-molecule inhibitors.[3] These include *NRAS* mutations, *GNAQ/GNA11* (detected in less than 1% of all melanomas but more than 80% of uveal melanomas, *CKIT* (detected in less than 6% of all melanomas but enriched in acral and mucosal melanomas), and loss of *NF1*. Not surprisingly, MEK inhibitors have been, and are currently being, studied extensively in these patients. Additionally, newer agents such as pan-RAF and ERK inhibitors have shown preclinical activity in melanoma and have now have entered the clinic and are currently being evaluated in phase I trials (NCT02014116, NCT01781429, NCT01875705).[71-78]

Targeting Uveal Melanoma

Uveal melanoma is a deadly disease that is often associated with metastatic involvement of the liver and lungs despite successful treatment of the primary tumor with surgery or stereotactic radiation techniques. Mutations in *GNAQ* and *GNA11* are present in the great majority of cases and predict signaling through protein kinase C (PKC), the MAPK pathway, and the PI3K pathway. In fact, preclinical evidence supports the use of inhibitors of MET, MEK, PKC, and PI3K/

AKT/mTOR, either as single agents or in combination.[79-87] In the clinic, single-agent MEK inhibition has been tested in a randomized phase II trial compared to chemotherapy (either dacarbazine or temozolomide) in 120 patients with metastatic uveal melanoma and was associated with an improved response rate (14 vs. 0%) and PFS (15.9 vs. 7 weeks, hazard ratio [HR] 0.46, p < 0.001) compared to chemotherapy, but showed no significant improvement in OS (11.8 vs. 9.1 months, HR 0.66, p = 0.09).[88] Building on the single-agent MEK inhibitor data, a randomized phase II trial of the MEK inhibitor trametinib and the AKT inhibitor GSK2141795 (NCT01979523) is currently ongoing. Targeting PKC signaling with the PKC inhibitor AEB071, either as a single agent (NCT01430416) or in combination with a MEK inhibitor (NCT01801358) or PI3K inhibitor (NCT02273219), is another strategy that is being testing in the clinic. Last, a number of trials of MET inhibitors are ongoing and currently enrolling patients with uveal melanoma, including the randomized phase II trial in the Alliance intergroup comparing the MET inhibitor cabozantinib with chemotherapy (NCT01835145).

Targeting CKIT

A number of inhibitors of CKIT have been tested in melanoma, with varying results. The first was a phase II trial of imatinib that enrolled 26 patients with metastatic melanoma independent of mutation or amplification status.[89] In retrospect, it is not surprising that there were no responses to therapy in this initial study; however, in three subsequent clinical trials of imatinib in patients with mucosal or acral melanoma, responses were seen in 17% to 29% of patients.[90-92] Responses were observed in nearly 30% of patients with *CKIT* mutations or amplifications, particularly in either exon 11 or 13. Phase II trials of nilotinib (NCT00788775, NCT01099514, NCT01028222), dasatinib (NCT00700882), and sunitinib (NCT00577382) have either completed accrual or are ongoing.

Targeting NRAS

Activating mutations of *NRAS* are the second most common oncogenic mutations in melanoma and are present in 20% to 30% of patients with cancer associated with MAPK activation.[3,8] As such, targeting mediators of this pathway is a logical approach that is supported by preclinical evidence; pan-RAF inhibitors, MEK inhibitors, and ERK inhibitors all have substantial preclinical activity in these tumors.[71,72,77,78] The MEK inhibitor binimetinib is associated with a 20% response rate and 4.8-month PFS in *NRAS*-mutant patients.[93] Based on these data, a randomized phase III trial comparing binimetinib with dacarbazine is underway (NCT01763164) and positive results would change the standard of care for this patient population. A randomized phase II trial of the MEK inhibitor pimasertib compared to dacarbazine has completed enrollment (NCT01693068).

Despite promising early clinical data, it is clear that the majority of patients with *NRAS*-mutant melanoma will either not benefit, or will only transiently benefit, from treatment with MEK inhibitors.[93] Thus, strategies to overcome either intrinsic or acquired resistance to MEK inhibitors are needed. In a seminal preclinical experiment, Kwong et al performed comparative analysis of *NRAS*-mutant melanoma tumors treated with vehicle, MEK inhibitor, and NRAS extinction. They determined that CDK4 was the top pathway regulator in the MEK-treated model, but not in the NRAS extinction model.[94] In other words, CDK4 expression was identified as a top candidate for mediating MEK inhibitor resistance in *NRAS*-mutant melanoma. Proving this point, dual MEK and CDK4/6 inhibitor therapy was more effective than either agent alone in multiple NRAS xenograft models.[94] Building on this work, a phase I trial of the MEK inhibitor binimetinib in combination with the CDK4/6 inhibitor LEE011 in patients with metastatic *NRAS*-mutant melanoma opened to enrollment and the preliminary data were presented at the American Society of Clinical Oncology's 2014 Annual Meeting.[95] Tumor regression was seen in most patients across all dose cohorts, responses were achieved in 7 of the 22 patients enrolled, and another 11 had stable disease. A similar trial evaluating the combination of trametinib/palbociclib is currently open for patients with all solid tumors (NCT02065063).

Targeting Angiogenesis

Tumor angiogenesis in melanoma has been well documented. Numerous molecules that promote angiogenesis are overexpressed in melanoma, including VEGF, PDGF, fibroblast growth factor (FGF), and interleukin 8.[96,97] Furthermore, their expression is associated with invasion and metastasis in preclinical models and may be associated with worse prognosis in patients with melanoma. Based on these findings and the effectiveness of angiogenesis inhibitors in other cancers (including renal cell carcinoma, breast cancer, and colon cancer), a number of antiangiogenic agents have been tested in patients with advanced melanoma. Bevacizumab, a monoclonal antibody targeting VEGF, has been evaluated in patients with melanoma with the most promising results seen for the combination of carboplatin/paclitaxel/bevacizumab. In an initial phase II trial of 53 patients, 9 (17%) patients achieved a partial response (PR) and an additional 30 (57%) had stable disease for at least 8 weeks.[98] Based on these results, a multicenter, randomized phase II trial was performed evaluating the combination of carboplatin/paclitaxel with or without bevacizumab. Specifically, 214 patients were enrolled via a 2:1 random allocation to receive carboplatin/paclitaxel plus bevacizumab (143 patients) or carboplatin/paclitaxel plus placebo (71 patients). The response rate (25.5 vs. 16.4%; p = 0.16), median PFS (5.6 vs. 4.2 months; p = 0.14), median OS (12.3 vs. 9.2 months; p = 0.19), and 1-year OS (53 vs. 39%; p = 0.06) were all better in patients receiving carboplatin/paclitaxel with bevacizumab; however, none of these findings were significant.[99] The addition of bevacizumab appeared to provide particular benefit with regard to improved OS in patients with M1c disease (HR for OS 0.64; 95% CI, 0.44 to 0.95), especially among patients who had elevated levels of lactate dehydrogenase (LDH; HR 0.53; 95% CI, 0.32 to 0.88).[99] The

TABLE 1. Clinical Trial Results of Targeted Therapy in Genetically Defined Patient Populations

Inhibitor(s)	Target	Trial Phase	CR + PR (%)	Median PFS/TTP (Months)	Reference
BRAF Mutant					
Vemurafenib	BRAF^V600	III	53	6.9	Chapman et al[28]
Dabrafenib	BRAF^V600	III	50	6.7	Hauschild et al[30]
Trametinib	MEK1/2	III	22	4.8	Flaherty et al[29]
Binimetinib*	MEK1/2	II	20	3.5	Ascierto et al[93]
Vemurafenib plus cobimetinib	BRAF^V600 and MEK 1/2	III	68	9.9	Larkin et al[33]
Dabrafenib plus trametininb	BRAF^V600 and MEK 1/2	I/II	76	9.4	Flaherty et al[31]
Dabrafenib plus trametininb	BRAF^V600 and MEK 1/2	III	67	9.2	Long et al[34]
Dabrafenib plus trametininb	BRAF^V600 and MEK 1/2	III	64	11.4	Robert et al[36]
DTIC plus selumetinib	MEK 1/2	II	40	5.6	Robert et al[111]
NRAS Mutant					
Binimetinib	MEK1/2	II	20	3.7	Ascierto et al[93]
Binimetinib plus LEE011	MEK1/2 and CDK4/6	I	33	N/A	Sosmna et al[95]
CKIT Mutant/Amplified					
Imatinib	CKIT	II	16	3	Carvajal et al[92]
Imatinib	CKIT	II	30	3.5	Guo et al[90]
Imatinib	CKIT	II	29	3.7	Hodi et al[91]

Abbreviations: CR, complete response; PR, partial response; PFS, progression-free survival; TTP, time to progression: N/A, not available.
*Some patients pretreated with BRAF inhibitor.

benefit of VEGF pathway inhibition in patients with M1c disease and elevated LDH has been suggested in other trials of antiangiogenic agents, including a phase III trial of carboplatin/paclitaxel with or without sorafenib (E2603) in which patients in this high-risk category showed a trend toward improved PFS and OS.[23,100]

THE PROMISE AND CHALLENGES FOR FUTURE THERAPY IN MELANOMA

Although targeted therapies represent a promising weapon in the armamentarium against melanoma, their effective use in the clinic is not without challenges. As previously mentioned, multiple mechanisms of resistance to targeted therapy, including genomic and phenotypic mechanisms, are observed among different patients, as well as within or between tumors in the same individual. Advanced cancers in particular show a great deal of genetic instability, resulting in the emergence of multiple metastatic clones, each with a different genetic profile and sensitivity to specific treatments.[101-103] Tumor heterogeneity and transcriptional plasticity have been implicated as drivers of resistance to targeted therapy in melanoma and represent a significant challenge to effective treatment of this disease.[103] Increased use of novel targeted therapy combinations in the future may help to overcome both inter- and intratumor heterogeneity by broadening the targeting spectrum and potentially increasing the probability of therapeutic effectiveness.[104] Unfortunately, partial or complete overlap of toxicities is common when taking a combinatorial approach, and must be taken into account when dose escalation rules are chosen. In many cases synergistic

toxicity will result, perhaps caused by nonspecific targets, requiring substantial dose reductions. For example, the combination of the selective MEK 1/2 inhibitor binimetinib with the CDK 4/6 inhibitor LEE01 demonstrated promising antitumor activity in patients with advanced *NRAS*-mutant melanoma, but also resulted in frequent adverse events that necessitated multiple dosing reductions and interruptions.[95] In general, however, combinations that target parallel pathways are less likely to have overlapping toxicity and may be better tolerated, as are agents with greater specificity.[105] For example, the combination of the BRAF inhibitor dabrafenib with the MEK inhibitor trametinib in patients with *BRAF*-mutant melanoma showed a decrease in many class-related toxicities associated with BRAF inhibitors compared to dabrafenib monotherapy.[31,105,106]

As novel targeted therapies continue through development, the translation of preclinical data into the clinical setting is often difficult. Cell lines and animal models may not effectively mimic human tumors, the tumor microenvironment, or immune responses, and may not demonstrate the same mechanisms of resistance. For novel drug combinations, this translation can be fraught with complications if laboratory and animal models used for one class of agents differ from those used for another.

Identifying appropriate biomarkers is critical for the detection, treatment, and monitoring of targeted therapies. Biomarker identification and analysis has typically relied on the use of tumor tissue, which involves a great cost, logistical difficulties, and risk to the patient. The continued development of noninvasive tools such as circulating tumor DNA (ctDNA) will be important for use as a tissue surrogate for a

variety of different solid tumor types and clinical indications, in addition to opening the possibility of regular monitoring of patients and changing treatments as necessary.[108] However, even if clinically relevant biomarkers and actionable mutations are discovered, there may not be a matched agent in development that effectively targets them.

The use of novel targeted combinations is also complicated by the many different motivations of the various stakeholders involved in drug development, including pharmaceutical companies, academic researchers, and regulatory agencies.[105,109,110] All too often, these stakeholders have different priorities, such as intellectual property, conflict of interest, incentives for academics, and publication policies. Different views on these priorities can lead to distrust, a decision not to collaborate, and eventual failure of a project. Lack of collaboration can lead to duplication of efforts and lack of progress, resulting in inefficient use of limited patient and financial resources.[105] Finding a way to satisfy these different priorities is critical in order to move therapies forward in the most efficient manner possible.

CONCLUSION

Although not without challenges, the use of novel targeted therapies in the context of molecular testing has opened new avenues for a precision medicine approach for metastatic melanoma, including a significant benefit already realized for this patient population. In some cases impressive tumor regressions have been demonstrated (Table 1); however, responses are not seen in the majority of patients with non-*BRAF* mutated cancer who are treated with targeted therapy and relapse is frequent in such cases despite combination therapy with BRAF and MEK inhibitors. Intensive translational research has highlighted the complexity of the resistance mechanisms involved and offers opportunities for interventions and improved patient outcomes. There is a need for additional clinical trials accompanied by high-throughput biomarker analyses to further improve these outcomes. Overcoming the scientific challenges, as well as satisfying the priorities of the various stakeholders involved in the development of novel therapies, will be critical for improving the treatment of patients with melanoma.

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Challenges in Managing and Coordinating Care in Different Settings for Geriatric Patients with Cancer

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Treating Older Adults with Cancer: Geriatric Perspectives

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OVERVIEW

The proportion of older adults (age 65 and older) in oncology practices continues to increase. Older adults present with unique issues that complicate management decisions and evidence from randomized clinical trials to inform management of these patients is lacking. Despite this, principles of geriatric medicine need to be incorporated into oncology practice to provide optimal individualized care to patients. There is increasing evidence from observational studies that geriatric assessment (GA) strategies can be applied in oncology, can help predict treatment outcomes, and can inform supportive care management for older adults. In this review, we discuss the principles of GA and their use in older adults with cancer. In addition, considerations on when to refer to a geriatrician and issues related to management of vulnerable older adults will be addressed.

The baby boomers began turning age 65 in 2011, leading to a doubling in the U.S. population age 65 and older by 2030.[1] At the same time, life expectancy is increasing. By 2030, the largest growth in the U.S. population will occur among individuals aged 80 and older. This demographic shift correlates with a rise in age-related diseases, such as cancer. The majority of cancer diagnoses and cancer deaths occur in individuals aged 65 and older. A 67% increase in cancer incidence among individuals age 65 and older is predicted to occur from 2010 to 2030.[2] Furthermore, most cancer survivors are older adults, who live with the sequelae of a cancer diagnosis and its treatment in the setting of aging and age-related diseases.

The growth in the number of older adults with cancer and cancer survivors occurs at a time when there is also an anticipated physician workforce shortage. The number of physicians who are specializing in geriatric medicine is decreasing.[3] Furthermore, there are not enough oncologists to care for this growing population of older adults in need.[4] The Institute of Medicine (IOM) report *Retooling for an Aging America: Building the Health Care Workforce* stated: "The health care workforce in general receives very little geriatric training and is not prepared to deliver the best possible care to older patients."[3] Currently, 1% to 2% of physicians and less than 1% of nurses, physician assistants, and pharmacists have geriatric specialization or certification. The IOM report highlighted that "… to meet the health care needs of the next generation of older adults, the geriatric competence of the entire workforce needs to be enhanced … innovative models need to be developed and implemented." This article will review some of the key considerations in caring for an older adult with cancer, including individualizing care for older adults with cancer through utilization of a GA and considerations on when to refer to a geriatrician.

INCORPORATING GERIATRIC ASSESSMENT INTO DECISION MAKING

Care of the geriatric patient (like the pediatric patient) requires a unique skill set. For both the pediatric and geriatric patient, there are age-related changes in physiology that increase vulnerability to toxicity, highlighting the concern regarding long-term effects of therapy. However, there is a unique difference between the geriatric and pediatric populations. For the pediatric patient, chronological age closely mirrors functional age. In contrast, there is a wide heterogeneity in chronological age and functional age in the geriatric patient.

A key part of decision making in the geriatric patient with cancer is to understand the individual's functional age in order to personalize care. A GA is a tool that can be utilized to achieve this goal through an evaluation of key domains predictive of morbidity and mortality risk in older adults, including functional status, comorbid medical conditions, cognition, psychological state, social support, nutritional status, and a review of medications.[5-11] This type of assessment can predict an older adult's life expectancy[8,12-15] and risk for chemotherapy toxicity.[16-20] Importantly, brief GA tools that are primarily survey based can be performed in oncology clinics. Useful chemotherapy toxicity risk scores have been developed from observational studies that can be applied in practice.[17,20] These studies highlighted specific patient char-

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TABLE 1. Characteristics Associated with Chemotherapy Toxicity among Older Adults with Cancer

Study (No. of Patients)	Physical Limitations	Sensory Impairment	Cognitive Impairment	Depressive Symptoms	Nutrition	Polypharmacy
Hurria et al[20] (500, mixed sample)	√	√				
Extermann et al[17] (510, mixed sample)	√	N/A	√		√	
Aparicio et al[16] (123, colon)	√	N/A	√			N/A
Freyer et al[18] (83, ovarian)	√	N/A		√		
Hamaker et al[19] (73, breast)	N/A					√

Abbreviations: N/A, not assessed.

acteristics that are independently associated with toxicity and show that the cumulative burden of impairments is prognostic (Table 1). Most importantly, a GA can identify areas of vulnerability and can be utilized to guide interventions. The domains of a GA are reviewed below, with a focus on specific pertinence to the care of older adults with cancer.

Functional Status

A functional status assessment focuses on the need for assistance with daily activities to maintain independence in the home (Activities of Daily Living [ADL]) and in the community (Instrumental Activities of Daily Living [IADL]). Activities of Daily Living include basic self-care skills such as bathing, dressing, toileting, transferring, and maintaining continence. IADL are activities needed to maintain independence in the community such as shopping, taking transportation, preparing meals, doing housework, taking medications, and managing personal finances. Among the geriatric population, the need for assistance with these activities is predictive of overall life expectancy and resource requirement (such as nursing home placement).[21] For the older patient with cancer, understanding the need for assistance with these activities is critical for treatment planning. For example, an integral part of cancer treatment is the use of sup-

portive care medications that are taken at home to minimize treatment side effects. A key part of a geriatric assessment is to evaluate whether the patient can take their medication at the right doses and at the right time. If not, then interventions can be implemented such as engaging family or a visiting nurse to assist. In addition, before prescribing chemotherapy, a transportation plan needs to be discussed. Some chemotherapy side effects, such as fever and neutropenia, can be life-threatening and require immediate attention. Key questions include whether the patient has transportation to clinic visits and whether they have a caregiver to provide transportation if they are not feeling well.

A part of functional assessment is to evaluate for the risk for falls. Falls in older adults account for many hospital admissions and, even without apparent injury, are a warning sign for impending functional decline. Falls can result in immobilization and disablement even if the patient does not sustain a fracture. These risks are even greater in older adults with cancer, especially if there is metastatic disease to bone or use of cancer treatments that accelerate bone loss. Furthermore, cancer or cancer treatments can be associated with platelet disorders and thrombocytopenia. Older adults with cardiovascular disease may already be on anticoagulants, further compounding risk. A fall can cause disastrous intracranial bleeding. Falls are predictable by any of the short directly observed tests of gait and balance that typically take less than 2 minutes and can be built into the patient check-in procedure.[22]

Comorbidity

An assessment of comorbidity is an integral part of cancer treatment planning. It is particularly important for older adults, due to the increased prevalence of multiple chronic conditions with age and the variability of comorbidity burden among similarly aged older adults. First, it can be utilized to assess overall life expectancy and to weigh competing causes of morbidity and mortality.[23] Second, it can be utilized to tailor cancer treatment. Key questions include whether the patient's other medical problems affect the ability to tolerate cancer treatments. For example, in a patient with diabetes, supportive care medications, such as steroids, may exacerbate diabetes. If steroids will be used, education and blood sugar management need to be considered. Furthermore, the choice of chemotherapy may be influenced by diabetic com-

KEY POINTS

- Oncologists need to be familiar with practical strategies to assess physiologic and functional capacity in older patients to inform optimal management.
- Geriatric assessment can predict treatment outcomes.
- Incorporation of geriatric assessment strategies and geriatric medicine consultation can help individualize initial treatment decisions and inform management strategies during the course of treatment and survivorship.
- Dose modification for vulnerable older adults reviewing palliative therapy is common and may optimize therapeutic benefit for some patients.
- Consideration of patient-centered outcomes inclusive of functional independence, health care utilization, and psychosocial health are critical for clinical trial design and to inform management of older adults receiving chemotherapy.

plications. For example, one may choose to avoid chemotherapy drugs that increase the risk for neuropathy (such as taxanes).

Cognition

With aging, there is an increased prevalence of cognitive impairment that poses distinct risks when considering cancer therapy.[24] The findings of cognitive impairment can be subtle and easily missed, but may be unmasked during a stressor such as cancer treatment. Studies suggest that the prevalence of cognitive impairment among older adults receiving chemotherapy may be 20% or greater.[25-27] Even mild cognitive impairment increases the risk for delirium, the risk for being unable to follow instructions for self-management of toxicities, the risk for nutritional depletion, and the ability to communicate important personal information to caregivers. A key component of assessing cognitive function is evaluating capacity for decision making. Even in the setting of cognitive impairment, individuals could have the capacity to make medical decisions if they meet the following four criteria: (1) understands the relevant information, (2) appreciates the situation, (3) uses reason to make a decision, and (4) communicates their choices.[28] Careful attention to cognitive status should be given at every clinical contact. Any abnormality on any of the short screening tools warrants further attention and referral.

It is important to recognize that screening for cognitive impairment may help identify delirium among older patients with cancer, especially during acute illness and treatment stress. Delirium is an acute, fluctuating disorder of attention that is common among acutely ill and postoperative older adults including those on inpatient oncology units.[29,30] Presence of delirium increases the risk for mortality. The agitated form is easily recognized, but the hypoactive form is easily overlooked if there is not a concerted effort to screen. There is some evidence that delirium is preventable with specialized acute care for the elderly teams.[31] Recognition of delirium provides an opportunity to identify and treat underlying causes (commonly infection, medications, or stress) and, potentially, prevent common complications including falls, malnutrition, aspiration, decubitus ulcers, and deconditioning.

Nutrition

Poor nutrition has been identified as a risk factor for chemotherapy toxicity.[17] Some simple screening questions for nutrition can include whether the patient has a low body mass index (less than 22 kg/m^2) or whether they had unintentional weight loss (greater than 5%). Patients with either a low body mass index or unintentional weight loss should be referred for a nutrition consult. Other standardized screening tools such as the Mini Nutritional Assessment can be readily implemented in routine practice.[17] If an older adult with cancer is fatigued or sick, they will need additional family or friend support to prepare meals. Therefore, assessing social support is an important part of the GA.[32,33] National programs such as the Meals On Wheels Association of America could also be implemented for those with inadequate social support.

Psychological State and Social Support

The psychological assessment includes an evaluation for depression, anxiety, and distress. These symptoms can be under-appreciated in older adults and sometimes present in unique ways with more somatic symptoms. Depression is, unfortunately, underdiagnosed in patients with cancer. Older adults were historically reluctant to admit to depression for fear of the social stigma associated with the diagnosis. However, the current generation of older adults was brought up in a different era in which the discussion of emotional states is far more permissive. Nonetheless, depression can go unnoticed in an office or bedside visit focused on somatic symptoms. Short validated tools such as the National Comprehensive Cancer Network Distress Thermometer or the question, "Do you feel depressed?" can facilitate screening and identification of those in distress.[34]

Gauging social support is a critical part of cancer treatment planning.[35,36] Key questions include evaluating whether the patient has both emotional support and tangible support. An example of emotional support is whether the patient has someone to listen to their problems and provide advice. An example of tangible support is whether the patient has someone to take them to the doctor if needed. In addition, one must assess if the patient is a caregiver for someone else, and who in turn will take on that caregiving role if the patient is too ill to do so.

Medication Review

Medication review and reconciliation are a key part of a GA. Older adults often take several medications prescribed by different health care providers, increasing the risk for medication duplications, dosing errors, and drugs inappropriate for older patients.[37-39] Older patients with cancer are taking an average of five medications or more.[25,40,41] Use of multiple medications at the time of chemotherapy treatment may increase the risk for toxicity because of adverse drug events or interactions. Studies investigating the prognostic significance of polypharmacy on treatment outcomes among older patients with cancer have shown mixed results. Most studies that incorporated polypharmacy as a risk factor in the context of a GA have not shown a clear association between number of medications and treatment toxicity.[17,26,42] These study cohorts are typically heterogeneous and include mixed cancer types and varied treatments. In a study of older women with advanced ovarian cancer, use of six or more medications at chemotherapy initiation was associated with decreased survival.[18] A study of older women with advanced breast cancer receiving chemotherapy showed use of five or more medications was independently associated with treatment toxicity.[19] Finally, among older adults with acute myeloid leukemia use of four or more medications at the time of induction chemotherapy was associated with increased early death, lower remission rates, and shorter survival.[43] Taken together, the current data suggest that the implications of polypharmacy may be specific to the clinical scenario and most evident in patients at high risk for toxicity.

Although polypharmacy may be a surrogate marker for unmeasured vulnerability, it also increases the risk for drug interactions during treatment. One study of older patients with cancer identified potential drug problems in 62% of patients with 50% of these rated as moderate or severe.[41] Another study of older adults receiving chemotherapy identified a potential drug interaction among 75% of patients (244 patients) and found an association between potential drug interaction and nonhematologic toxicity.[44] Although much more research needs to be done on this topic, proactive management strategies can be advocated to minimize risks for patients. Careful review of medications, including consideration of discontinuation of any medications without clear indication, may benefit many older adults. This is frequently an overlooked opportunity in oncology practice and may be facilitated by communication with a primary care physician or geriatrician. Use of available drug interaction software can help avoid initiation of new high-risk medications.

COLLABORATION WITH GERIATRIC MEDICINE
Who
There is a referral bias for the healthiest older adults to be referred for cancer treatment. Few clinical trials enroll older adults and those that do preselect for the fittest patients.[45] Until there is sufficient observational experience with a protocol or there are trials specifically designed for older adults, clinical oncologists will have to base judgments on individualized assessments.[46] Most physicians will be able to recognize the frailest patients without special tools. At first presentation these patients may report feeling weak, having little physical activity, and tiring easily. They may report poor appetite and some weight loss that cannot be attributed to the cancer or the cancer treatment.[47-49] The frail phenotype portends loss of organ reserve and loss of homeostatic capacity because of multiple accumulated deficits in many organ systems. In other words, it is not one organ, it is the integration of the systems of organs. Frailty manifests itself, therefore, in syndromes such as delirium, falls, and incontinence.[50]

Under the rubric of patient safety and quality improvement many U.S. hospitals and clinics now use rapid screens built into their electronic health records intake forms that ask straight forward functional questions to identify patients at risk for adverse hospital events, notably falls, delirium, early readmission and functional decline. Questions include: Do you have any visual or hearing problems? Have you fallen? Do you need help getting dressed, bathing, or getting your meals? Do you need help making decisions about your health care or finances? There are several population-validated short geriatric screening tools that have been piloted in geriatric patients with cancer with good predictive value when compared with a GA.[51-53] A screening questionnaire such as the VES-13 or G8 is usually self-administered in 5 minutes. These standardized questionnaires accurately identify older adults who would benefit from a more thorough assessment, coupled with targeted interventions, as part of treatment planning.

The GA has been shown repeatedly to identify older adults at high risk for unexpected treatment toxicity.[20,54,55] By and large, however, it turns out that all of the screening questions are not necessary to identify those at risk. Certain items seem to carry more weight, specifically those focusing on functional limitations in performing higher order activities. These include IADLs, which are those that are required to live alone.[20] In part, this is evidence for the referral bias that prevents the oldest, sickest, frailest patients from presenting to oncology practice. Many of the geriatric tools are designed to make fine distinctions among very frail older adults who may never be referred for cancer treatment. Therefore, the tools that work the best are those that can identify older adults who are functioning well at baseline, but they are doing so by compensating for an underlying deficit, the so-called vulnerable elderly. One study found that only 20% of older adults with a Karnofsky Performance Score (KPS) of 80 or higher performed perfectly on a 3- to 4-minute directly observed test of gait and balance.[56] A similar short observational tool predicted falls in older men attending a prostate cancer clinic.[57] Directly observed performance predicted disability and survival among older adults living in the community with a cancer diagnosis.[58] GA accurately predicted which of 68 older adults enrolled in a dose-escalation study were able to complete the regimen (fit), did not tolerate full-dose therapy (vulnerable), or were unable to complete the study because of excess toxicity (frail.) As expected GA did not predict which specific toxicity was limiting treatment, only that patients had predictable intolerance of symptoms.[59]

When
At present, most studies report on GA or other assessments shortly after diagnosis to predict how older patients will tolerate first-line therapy. However, we would argue that some aspects of the GA should be repeated at each visit. Toxicity is cumulative, and patients often minimize discomfort unless they are directly asked. This is a major part of the rationale for having supportive and palliative care for symptom control and for help in disclosing bad news.[60] Some toxicities, however, may be less obvious, such as delirium, neuropathy affecting gait and balance, drug interactions, depression, and bowel or bladder dysfunction. Very little has been published about the functional trajectory of older adults with cancer even though KPS or Eastern Cooperative Oncology Group (ECOG) Performance Status scores are routinely recorded. As demonstrated in several studies, these scales are global, impressionistic assessments that may miss key items of relevance to the geriatric population.

Where
Several research reports now show that gathering GA data on all older adults and following it with a routine or unsolicited consultation has an effect on cancer treatment decisions; however, several questions remain regarding how to best integrate GA and consultation into oncology care. In a recent systematic review summarizing the effect of geriatric evaluations on treatment decisions, a modification in treatment

plan was prescribed in almost 40% of patients, with less intensive treatment accounting for two-thirds of these plans.[61] In one French study, GA followed tumor board deliberation for the initial treatment of 191 patients older than 70. There was a slight tendency to decrease the intensity of treatment after reviewing the GA findings, but it is not clear from this report how the geriatric consultation was integrated into the final treatment plan.[62] A second French study introduced inpatient GA for hospitalized older adults with cancer.[63] Of 107 patients, the geriatric consultant agreed with the oncology treatment plan 68% of the time. When there was disagreement, approximately half of the time the oncology team ignored the geriatrics recommendations, whereas, the other half of the time the oncology team stepped down the treatment or changed to palliative care in concordance with geriatrics recommendations. Interestingly, a recent meta-analysis of the effect of inpatient geriatric consultation in a general hospital population concluded that the main benefit was to be seen in decreased mortality 6 to 8 months after discharge, not necessarily during the index admission.[64] In other words, it seems that geriatric inpatient consultation can help oncologists identify and plan care for the frailest and sickest patients on the one hand, and help with postacute care and planning as they do with any other hospitalized older adult.

In the outpatient setting, where most cancer treatment is delivered, GA has followed oncology assessment in two recently published reports. One clinic planned to refer all patients with gastrointestinal and lung cancer older than age 70 to the geriatrician for a GA. However, the actual referral rate was only 29%, and only 25% actually completed the appointment. The GA information affected only those patients for whom the oncologist had not decided what to do.[65] We see a different result in a report of geriatric consultation in an outpatient oncology setting in which patients were already receiving their first-line therapy.[66] Of 161 patients older than age 70, 49% had their treatment changed based on the geriatricians' assessment of ADLs, cognitive function, depression, and malnutrition: 34 had less intense treatment and 45 had more intensive treatment after consultation.

Why

Geriatricians anticipate, diagnose, and manage syndromes that do not necessarily involve only one organ, for which there is no diagnostic test, and for which there is ample evidence of increased morbidity, mortality, and disablement. Older patients who have these syndromes, whether at home or in the hospital, may end their lives in nursing homes or suffer other preventable losses in dignity and quality of life.

Current evidence supports the value of geriatric medicine consultation for at least some older adults with cancer. Consultation should be sought when validated screening tools indicate a problem with performing daily activities required for self-care (ADLs) and maintaining a household independently (IADLs). Consultation should be considered for older adults with polypharmacy, particularly in the setting of multimorbidity, frequent falls, and any change in mental status

that could indicate delirium or depression. Before treatment, older adults can be assessed for decisional capacity formally or informally. A rapid gait screening should be performed initially for risk stratification and, subsequently, to monitor risk for falls.

The timing of consultation remains in the hands of the primary oncology team. When oncologists have hesitation to treat and geriatric consultation is easily available, cancer treatment plans may be adjusted, more often toward less aggressive treatment. Hospital-based geriatric consultation can also be beneficial. The assessment of functional status, cognitive status, decisional capacity, physical performance, and emotional well-being should be considered vital signs to be followed throughout cancer treatment. Involving a geriatrician can help lessen the demands on the oncology team and potentially improve treatment outcomes.

THE EVIDENCE GAP BETWEEN RISK ASSESSMENT AND MANAGEMENT

Although there is increasing evidence that vulnerability to treatment toxicity can be predicted for older adults receiving chemotherapy,[17,20,27] there remains an evidence gap between identification of vulnerability and knowledge of how to best manage vulnerable older adults. Unfortunately, most randomized clinical trials are not yet incorporating measurement of vulnerability or frailty to inform which treatment modifications, if any, would optimize outcomes for a given older adult. The remaining sections of this chapter will highlight issues related to chemotherapy dosing and toxicity assessments among older patients in practice.

DOSE MODIFICATION FOR OLDER ADULTS RECEIVING CHEMOTHERAPY

Most published models to predict chemotherapy toxicity among older adults have shown that the risk of grade 3 to grade 5 toxicity for older adults is approximately 50%,[20] with vulnerable and frailer patients likely exceeding these estimates. When considering a treatment decision, the balance between the risk of treatment and its potential benefits often poses a major challenge. Treatment characteristics that have been shown to influence toxicity risk include use of standard-dose chemotherapy and polychemotherapy.[20] Therefore, dose modification is often considered to minimize the negative consequences of therapy on symptoms and quality of life. Because of a scarcity of clinical trial data there remain more questions than answers regarding the benefits and risks of dose modification strategies, particularly in the setting of first-line treatment for advanced cancer.

DOSE MODIFICATION IS COMMON AMONG OLDER PATIENTS WITH CANCER

Available evidence suggests that dose modification is common among older adults treated for cancer. Data from com-

munity practices have shown that increased age is associated with lower relative-dose intensity during adjuvant chemotherapy.[67,68] An analysis of a multisite cohort study enrolling older adults starting a new chemotherapy regimen showed that almost one-third (29%) of the 319 patients with advanced cancer had a dose reduction with the first cycle of chemotherapy. Factors associated with primary dose reduction included older age, a primary diagnosis of lung cancer, and comorbid conditions.[69]

INDICATIONS FOR UP-FRONT DOSE ADJUSTMENT

Physiologic changes associated with aging have implications for chemotherapy toxicity among older adults. Aging is associated with decreased intestinal absorption, changes in volume of distribution, decreased hepatic metabolism, and impaired renal excretion. The degree to which any of these changes occur in an individual and have clinical significance varies among patients of the same chronologic age. Among these, a decline in renal function needs to be considered in dosing. Many chemotherapy drugs are cleared renally and it is well documented that relying on serum creatinine alone will greatly underestimate renal function in older adults. Creatinine clearance should be calculated for all older adults starting chemotherapy treatment to inform dose adjustment for renally cleared drugs. Guidelines exist for recommendations on renal dose adjustment including a position paper published by the International Society of Geriatric Oncology.[70]

Current guidelines do not recommend up-front dose adjustment in the adjuvant setting for older adults because of the potential negative consequences on cancer outcomes and the goals of therapy. In this setting, the treatment decision should be framed around the question, "Do I think my patient can tolerate a standard dose regimen?" Mitigation of toxicity risk in the adjuvant setting may include a choice between standard-dose, single-agent chemotherapy compared with polychemotherapy in certain settings (i.e., colorectal cancer) or two-drug compared with three-drug combinations (i.e., breast cancer). Tailoring choice of regimen and supportive care to the patient's comorbidity profile may also minimize adverse events. For those patients considered unfit for standard-dose treatments, no adjuvant therapy is likely the best alternative. However, in the metastatic setting, our goals of treatment are to balance disease control and quality of life. Alterations in dosing and scheduling of treatments become an important strategy for the management of patients.

CLINICAL TRIAL EVIDENCE FOR DOSE MODIFICATION IN ADVANCED CANCER

Few randomized controlled trials have addressed the risks and benefits of up-front dose modification or treatment schedule modifications (i.e., treatment holidays) for non-fit older adults with advanced cancer, resulting in a paucity of guideline-based recommendations. However, several colon cancer trials directly or indirectly provide some insights into these approaches.

A novel randomized trial published by Seymour et al addressed, in part, the issue of dose reduction in first-line treatment for older adults with advanced stage colorectal cancer. This study used a 2-by-2 factorial design to randomize 459 frail (considered not fit for full-dose combination chemotherapy by their physician) older adults with metastatic colorectal cancer to one of four first-line systemic therapies using an attenuated starting dose (80% of standard).[71] The study design allowed for escalation to full-dose therapy after 6 weeks, if tolerated. Patients (median age 74) were randomly assigned to one of the following arms: (1) 48-hour intravenous fluorouracil (5-FU), (2) oxaliplatin/5-FU, (3) capecitabine, or (4) oxaliplatin/capecitabine. In addition to a quality-of-life questionnaire, a composite outcome termed overall treatment utility was incorporated in an attempt to capture patient and physician satisfaction with the outcome of each treatment decision. Several lessons can be learned from this study. First, recruiting unfit patients to a randomized trial was feasible. Second, few patients achieved dose escalation, with almost half (49%) requiring additional dose reductions. Third, the unique trial design, inclusive of patient-centered endpoints, provided relevant information suggesting that use of oxaliplatin in this attenuated dosing schedule may provide a palliative benefit, whereas, capecitabine may be associated with more toxicity compared with 5-FU. This study provides evidence for considering up-front dose attenuation when treating non-fit older adults with metastatic colorectal cancer, and introduces additional outcome measures to help quantify the palliative benefit of therapy.

Questions regarding optimal dosing schedules, including treatment breaks, for older patients are also common. Again, few studies specifically have addressed this issue in older patients, yet, older patients are most likely to suffer debilitating consequences from ongoing therapy. For colorectal cancer, some data can be extrapolated from existing studies investigating chemotherapy-free intervals (CFI).[72-75] For patients fit enough to initiate combination chemotherapy, evidence would suggest that CFI have minimal effect on overall survival with some potential benefits in quality of life. Although only a fraction of patients enrolled in these studies were older than 75, there is suggestion of similar outcomes among older compared with younger patients when using this strategy.[74] It is reasonable to incorporate these data into treatment planning for older patients in an attempt to minimize the negative consequences of therapy on functional independence and quality of life.

TOXICITY ASSESSMENT: WHAT ARE WE MISSING?

Prediction of treatment outcomes for older adults is hindered not only by the limited number of older adults enrolled in clinical trials, but also by the lack of routine collection of endpoints that better describes the patient experience. Outcomes such as functional independence, health care utilization, psychosocial health, and well-being are typically not measured in trials. In a review of 127 older

patient–specific palliative chemotherapy trials, functional outcomes, health care utilization, cognitive function, and quality of life were reported in 6%, 3%, 6%, and 31%, respectively.[76] Yet many of these outcomes are of concern to patients. Use of GA measures during treatment can provide useful information to inform risk prediction and supportive care. For example, an observational study of 364 adults age 70 or older (77% with ECOG 0 to 1) starting first-line chemotherapy showed that almost 17% experienced a loss of independence defined by a decrease in the ability to complete ADLs after the first treatment.[77] Incorporation of simple assessment measures during treatment in clinical trials and in practice may better inform

management of complications to ultimately improve treatment efficacy and tolerance.

CONCLUSION
Caring for older patients with cancer presents unique challenges. Incorporation of GA strategies can help individualize initial treatment decisions and inform management strategies during the course of treatment and survivorship. Incorporation of GA strategies into clinical trial design will provide needed evidence to optimize therapy for vulnerable and frail older adults.

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PATIENT AND SURVIVOR CARE

Depression, Anxiety, Neuropathy, and Fatigue: An Update on the 2014 ASCO Survivorship Guidelines and How to Incorporate Them into Practice

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Chemotherapy-Induced Peripheral Neurotoxicity in Cancer Survivors: An Underdiagnosed Clinical Entity?

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OVERVIEW

Systemic chemotherapy is a cornerstone of the modern medical management of cancer, although its use is limited by toxicity on normal tissues and organs, including the nervous system. Long-surviving or cured people strongly require a high level of wellness in addition to prolongation of life (the concept of the quality of survival), but neurologic dysfunction can severely affect daily life activities. Chemotherapy-related peripheral neurotoxicity is becoming one of the most worrisome long-term side effects in patients affected by a neoplasm. The central nervous system has a limited capacity to recover from injuries, and it is not surprising that severe damage can determine long-term or permanent neurologic dysfunction. However, the peripheral nervous system also can be permanently damaged by anticancer treatments despite its better regeneration capacities, and the effect on patients' daily life activities might be extremely severe. However, only recently, the paradigms of peripheral neurotoxicity reversibility have been scientifically challenged, and studies have been performed to capture the patients' perspectives on this issue and to measure the effect of peripheral neurotoxicity on their daily life activities. Despite these efforts, knowledge about this problem is still largely incomplete, and further studies are necessary to clarify the several still-unsettled aspects of long-term peripheral neurotoxicity of conventional and targeted anticancer chemotherapy.

Over the last decades, improvement in early diagnosis, precise subtype characterization, and more effective treatment plans allowed clinicians to achieve complete cures or remarkable increases in long-term survival in patients living with cancer in developed countries. For instance, in the period from 1950 to 2010, overall cancer-related mortality adjusted for age decreased in the United States by more than two-thirds in young patients (i.e., younger than age 14), by more than 50% in patients through age 44, and by at least 25% through age 64.[1]

This improvement highlighted an emerging issue in cancer survivors, represented by the persistent side effects of cancer treatment. Among several cancer treatment–related side effects, neurotoxicity can be particularly severe and long lasting and can affect the quality of life (QoL) as well as the daily life activities of cancer survivors.[2,3] The peculiar characteristics and biology of neurons (e.g., high specialization, selective metabolism, incapacity to replicate) and the very limited possibility of the central nervous system (CNS) to effectively recover from severe and extensive damage make CNS neurotoxicity a well-known, critical medical problem. However, despite the better regeneration capacity of the peripheral nervous system (PNS), PNS neurotoxicity also can be severe and permanent.

Although physicians and patients are now well aware of chemotherapy-related PNS neurotoxicity, and although its occurrence generally can be easily recognized, several unset-

tled issue are still present in this field. First, the precise clinical manifestations and their incidence and severity are not always properly assessed, and the several tools used so far have very rarely been validated for this specific use. Second, the pathogenesis of the clinical signs of PNS damage is unknown for most chemotherapy-related conditions. Third, the available pharmacologic and nonpharmacologic strategies designed to limit the incidence and severity of chemotherapy-induced neurotoxicity are not particularly effective in most instances. Finally, the long-term course and reversibility of symptoms and signs have very rarely been investigated so far.[4-9]

Overall, the importance of chemotherapy-related toxicity caused by PNS damage is underestimated. This aspect is becoming increasingly important, and the National Comprehensive Cancer Network has recently expanded its survivorship guidelines to include long-term chemotherapy-induced peripheral neurotoxicity (CIPN).

PATHOGENETIC AND CLINICAL FEATURES OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROTOXICITY

To achieve a proper understanding of the long-term effects of CIPN, knowledge of the basic pathogenetic and clinical features related to the use of the different neurotoxic dugs is necessary.

The PNS is a common target for the neurotoxicity of several conventional chemotherapy drugs. This is mostly because of the less efficient blood–nervous system barrier in the PNS, namely at the dorsal root ganglia (DRG) level, which allows easy access to nerve fibers and neurons. However, the most recent cancer-targeted drugs also are not completely safe.[6] The peripheral neurotoxicity of both conventional and targeted compounds will be treated separately.

In most cases, CIPN ensuing after conventional treatments consists of dose-dependent, predominantly sensory, length-dependent neuropathies/neuronopathies. More rarely, motor, autonomic, or cranial nerve involvement also can be observed. The conventional drugs associated with CIPN are platinum compounds, taxanes, vinca alkaloids, epothilones, proteasome inhibitors, and thalidomide.

Patients with CIPN can experience negative (i.e., impairment in touch, pin and vibration perception, sensory ataxia with imbalance and falls) as well as positive (i.e., paresthesias/dysesthesias, neuropathic pain) symptoms. All of these symptoms generally develop at limb extremities and then show a distal-to-proximal progression. The frequency, severity, and time course of CIPN can be very variable. In patients with CIPN who are treated with platinum drugs, a peculiar temporal pattern can be observed, which is represented by symptoms that worsen months after chemotherapy suspension—the so-called coasting phenomenon. As it will be discussed later in more detail, it is now clear that CIPN-related signs and symptoms may be long lasting or even permanent. The typical clinical features of CIPN have been extensively reviewed (Table 1).[10-13]

The epidemiology of CIPN is still unclear, and one of the main reasons for this uncertainty is the lack of a gold standard in its assessment.[5] In fact, the reliability and reproducibility of a CIPN assessment in patients with cancer are still unmet clinical and scientific needs. In the past, several methodological issues were not clearly recognized, and different nonvalidated scales were used, which led to conflicting results. Despite these challenges, the proper design of a reliable assessment plan is now easier for patients with CIPN. In this clinical setting, a formal trial (the CI-PeriNomS study) demonstrated the actual reliability of physician-assessed and patient-reported outcome measures in patients with stable CIPN. However, the same demonstration is still missing for the responsiveness to changes during treatment and the clinical meaningfulness of these changes.

Moreover, the markedly different perception of CIPN severity using physician-assessed measures (e.g., the widely used National Cancer Institute Common Toxicity Criteria [NCI-CTC] adverse events scale and the more comprehensive Total Neuropathy Score, clinical version) or patient-reported outcome measures (e.g., the European Organisation for Research and Treatment of Cancer [EORTC] QLQ-C30 and CIPN20 modules) is emerging very clearly. The first methodological study designed to address this relevant issue has been reported recently,[4] and marked differences in perceptions of CIPN by patients versus by treating physicians have been demonstrated.[14] These apparently conflicting results actually represent two sides of the same coin, and they should always be coupled in the planning and interpretation of any study devoted to CIPN investigation or treatment.

CIPN pathogenesis is still unclear for many aspects, and most of the available information relies on the results of preclinical models.

The DRG are the main target of platinum drugs.[11] These drugs cause intrastrand adduct and interstrand crosslink formation with a subsequent alteration of the tertiary structure of the DNA in DRG neurons. They also cause cell-cycle kinetics alterations: postmitotic DRG neurons would reenter into the cell cycle and be induced into apoptosis.[15] Other pathogenetic hypotheses have been proposed, which involve oxidative stress, mitochondrial dysfunction, reduction in the activity of enzymes involved in DNA base excision, repair of oxidative damage, redox regulation, and cellular transport.[16-18]

The most obvious mechanism of PNS damage by taxanes is related to their hyper-polymerizing action on microtubules. In the axons, microtubule disruption can lead to interference in axonal transport, which eventually affects the integrity of sensory neurons. A dying-back process that starts from distal nerve endings and is followed by disturbed axonal flow has been demonstrated in models of CIPN associated with taxanes.[19] However, macrophage activation in both the DRG and the peripheral nerve, and microglial activation within the spinal cord, also have been demonstrated.[20] In an animal study, paclitaxel-induced swelling and vacuolation of axonal mitochondria in A and C fibers was demonstrated.[21]

Competition studies with paclitaxel demonstrated that epothilones might act on the same or on an overlapping binding site on tubulin. Kinetic experiments revealed that epothilones are competitive inhibitors of paclitaxel binding to the tubulin polymer. On this basis, it is likely that taxanes and epothilones share the same mechanism of damage.[11]

Vinca alkaloid neurotoxicity is probably related to their ability to inhibit microtubule functions and disrupt the cytoskeleton.[11] In neurons, vinca alkaloids prevent tubulin polymerization

KEY POINTS

- Anticancer chemotherapy can permanently damage both the central and the peripheral nervous systems, but the mechanism(s) of this toxicity is largely unknown.
- The recognition of chemotherapy-induced peripheral neurotoxicity is simple, if education is provided and a high level of attention is maintained.
- Chemotherapy-induced peripheral neurotoxicity is probably an underestimated clinical problem in cancer survivors.
- Patients' and health-care providers' perceptions of the severity of chemotherapy-induced peripheral neurotoxicity may be very different, as demonstrated by recent studies focused on this highly relevant issue.
- No effective treatments are available for alleviating persistent symptoms of chemotherapy-induced peripheral neurotoxicity.

TABLE 1. Typical Clinical Features of Chemotherapy-Induced Peripheral Neurotoxicity Associated with Standard Chemotherapeutic Agents

Drug	Typical Symptoms/Signs
Platinum	
Cisplatin	Early reduction/loss of DTR
	Distal, symmetric, upper- and lower-limb impairment/loss of all sensory modalities
	Sensory ataxia and gait imbalance are frequent
	Neuropathic pain can be present, but it is not frequent
	Coasting* phenomenon is frequent
Carboplatin	Similar to cisplatin but milder
Oxalipatin	Acute
	Cold-induced transient paresthesias in mouth, throat, and limb extremities
	Cramps/muscle spasm in throat muscle, jaw spasm
	Chronic
	Very similar to cisplatin
Bortezomib	Reduction/loss of DTR
	Mild to moderate, distal, symmetric loss of all sensory modalities occurs. Small myelinated and unmyelinated fibers are markedly affected, leading to severe neuropathic pain.
	Mild distal weakness in lower limbs is possible
Taxanes (paclitaxel, docetaxel)	Reduction/loss of DTR
	Myalgia syndrome is frequent (as an atypical neuropathic pain?)
	Distal, symmetric, upper and lower limb impairment/loss of all sensory modalities
	Gait unsteadiness is possible because of proprioceptive loss
	Distal, symmetric weakness in lower limbs is generally mild
Epothilones (ixabepilone, sagopilone)	Signs and symptoms are similar to taxanes, but neuropathic pain is less frequent, and recovery is reportedly faster
Vinca alkaloids (vincristine, other compounds with similar but much lower neurotoxicity)	Reduction/loss of DTR
	Neuropathic pain/paresthesia at limb extremities is relatively frequent
	Distal, symmetric, upper and lower limb impairment/loss of all sensory modalities
	Distal, symmetric weakness in lower limbs progressing to foot drop
	Autonomic symptoms (eg, orthostatic hypotension, constipation) may be severe
Thalidomide	Reduction/loss of DTR
	Relatively frequent neuropathic pain at limb extremities
	Mild to moderate, distal, symmetric loss of all sensory modalities
	Weakness is rare

Abbreviations: DTR, deep tendon reflexes.
*Coasting = worsening of signs/symptoms of neuropathy over months after drug withdrawal.

from soluble dimers into microtubules, which leads to axonal swelling and alteration of the axonal transport.[22] The different affinity for tubulin shown by vinca alkaloid compounds (vincristine affinity > vinblastine > vinorelbine > vinflunine) might explain the distinct neurotoxic profile of these drugs.[11]

DRG neurons, satellite cells, and nerve fibers also are targets of bortezomib toxicity.[23,24] In animal models, bortezomib causes a severe DRG neuronal dysfunction that not only inhibits proteasome activity but also alters transcription, nuclear processing and transport, and cytoplasmic translation of mRNA.[25] In the peripheral nerves, histopathologic and neurophysiologic findings demonstrate a dose-dependent damage of B and C fibers with abnormal vesicular inclusion bodies in unmyelinated axons.[23,24] Mitochondrial and endoplasmic reticulum damage and dysregulation of

neurotrophins, caused by either activation of the mitochondrial-based apoptotic pathway or inhibition of the transcription of factors necessary for neuron survival, also have been reported.[26] Recently, increased tubulin polymeration has been demonstrated in cultured DRG neurons and in animal models.[27,28]

Despite the evident neurotoxic effects of thalidomide,[29] no convincing pathogenetic explanation for thalidomide neurotoxicity has been provided, and its more recent and highly active derivatives lenalidomide and pomalidomide are definitely less neurotoxic.[30]

At the moment, no effective preventive or curative strategy is available for the treatment of CIPN, as documented by a systematic Cochrane review of platinum drugs.[31] A focused American Society for Clinical Oncology (ASCO) expert panel extended this review substantially to the

other neurotoxic drugs, with the same disappointing results.[32]

Conventional chemotherapy has limitations in its effectiveness, and it is associated with potentially severe side effects as a result of damage to normal tissues, as shown for CIPN. To overcome some of these problems, a transition to rationally designed, molecularly targeted drugs, which aims at a much more specific effect on cancer cells and a sparing of normal tissues, has occurred in chemotherapy. Several of these targeted drugs are now used routinely. Different from chemotherapy with curative intent, cancer-targeted drugs also are used as continuous administration after treatment response, and maintenance therapy can be continued in cases of tumor progression to prevent uncontrolled growth. Although these drugs are generally considered safer and less toxic than conventional chemotherapy, off-target toxicities (e.g., neurotoxicity) may emerge, particularly during prolonged use.

Although the literature evidence is still limited and data are somewhat inconsistent, PNS toxicity has been described. Moreover, because cancer-targeted therapies frequently are used after or in combination with conventional chemotherapy, the possibility that their use could worsen the toxicity profile of standard neurotoxic chemotherapy drugs also should be considered. In Table 2, examples regarding the possible peripheral neurotoxic effect of cancer-targeted drugs are reported.

Also, the pathogenesis of cancer-targeted drugs effects on the PNS is largely unknown. It has been suggested that some of their neurotoxic effects are a result of the capacity to interact with the immune system. For instance, five of a series of 85 patients treated with alemtuzumab developed a progressive sensorimotor radiculoneuropathy and/or a myelitis.[33] Moreover, in 2010, another case of acute inflammatory polyradiculoneuropathy (Guillain-Barré syndrome) was reported in an alemtuzumab-treated patient.[34] In these cases, it has been hypothesized that alemtuzumab may trigger an autoimmune cascade that results from indiscriminate dysregulation of regulatory T cells or from a molecular mimicry.

In addition to the immune-mediated effect on the PNS, clinical pictures compatible with classical CIPN also have been described with cancer-targeted drugs. The administration of brentuximab vedotin can be associated with a dose-dependent peripheral neuropathy that can limit prolonged administration of the drug. In phase I studies, cumulative dose-related peripheral neuropathy, probably associated with unconjugated microtubule inhibitor monomethyl auristatin E (i.e., the active part of the molecule acting as the classical chemotherapy drugs) was clinically relevant; 37% of patients showed persistent symptoms, which led to drug discontinuation in 25% of patients.[35] In another study, 73% of patients treated with brentuximab vedotin developed peripheral neuropathy, mostly mild to moderate, and similar data were replicated in phase II studies.[36] However, dramatic motor neuropathy also has been associated with brentuximab vedotin use.[37]

It can be concluded that careful monitoring that is based on a formal neurologic assessment of the possible PNS toxicity of all of these new drugs is mandatory to ascertain in prospective clinical trials their real toxicity profiles, alone or in combination treatments.

EVIDENCE OF LONG-TERM PERSISTENCE OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROTOXICITY

The previously accepted paradigm that CIPN, in nearly all cases, is a reversible clinical condition has recently been challenged by several studies performed mainly in patients with breast, colorectal, and ovarian cancer, in which the use of neurotoxic drugs is frequent and survival for greater than 5 years is increasingly frequent.

TABLE 2. Examples of Peripheral Neurotoxicity of Targeted Agents Used in Cancer Therapy

Drug	Reported Previous Neurotoxic Treatment	Description of Peripheral Nervous System Toxicity
Alemtuzumab	None	Progressive peripheral sensorimotor radiculoneuropathy and/or myelitis
Brentuximab vedotin	Previous chemotherapy (undefined)	Peripheral sensory neuropathy: any grade in up to 66%; grade 3 in up to 8%
		Peripheral motor neuropathy: any grade in up to 11%, grade 3 in up to 7%
Carfilzomib	Lenalidomide or thalidomide	Treatment-related neuropathy: any grade in up to 17%; rarely grade 3
Ibritumomab	CVP or COP or CHOP	Paresthesias: grade 1 in up to 13%
Imatinib	Cytarabine	"Pain in limbs": any grade in up to 11%; grades 3-4 in up to 1%
Ipilipumab	Carboplatin	Guillain-Barré syndrome
Lapatinib	Taxanes, vinorelbine	"Pain in extremities": any grade in up to 13%; grade 3 in < 1%
Regorafenib	Oxaliplatin	Sensory neuropathy: any grade in up to 7%; grade 3 in < 1%
Rituximab	CHOP (first-line), ProMACE CytaBOM (second-line)	Guillain-Barré syndrome
	None	Guillain-Barré syndrome
Sorafenib	Previous chemotherapy (undefined)	Treatment-emergent sensory neuropathy: grades 1-2 in up to 20%
Vemurafenib	Previous chemotherapy (undefined)	Peripheral neuropathy: any grade in up to 10%; grade 3 in 1%
Vorinostat	Previous chemotherapy (undefined)	Cutaneous polyneuropathy (tingling) was reported as leading to discontinuation

Abbreviations: CVP, cyclophosphamide, vincristine, prednisone; COP, cyclophosphamide, vincristine, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; ProMACE CytaBOM, cyclophosphamide, doxorubicin, etoposide cytozar, bleomycin, vincristine, methotrexate, prednisone.

The availability of large registries of patients with cancer who were carefully observed—such as the Patient-Reported Outcomes Following Initial Treatment and Long-Term Evaluation of Survivorship (PROFILES) registry—has allowed investigations on the persistence of CIPN-related long-term effects in several cancer types and, therefore, on the relationship existing with different treatments.

In patients with colorectal cancer treated with oxaliplatin, Park et al reported the persistence of CIPN symptoms in 79% of patients after a median follow-up of 29 months; after a similar period, in a different study, Gramont et al reported more than one-fourth of the patients with NCI-CTC grade 3 CIPN still had symptoms.[38,39] The prevalence of NCI-CTC grades 1 to 3 CIPN was 24% after 18 months in the Multicenter International Study of Oxaliplatin/Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) clinical trial.[40] Analyzing the PROFILES data, Mols et al evaluated the features of long-term CIPN-related symptoms in 500 survivors of colorectal cancer treated with chemotherapy assessed with the EORTC CIPN20 scale,[41] a patient-reported outcome that is based on separate instrument reporting for sensory, motor, and autonomic symptoms. In the study, the persistence of CIPN-related symptoms was demonstrated for up to 11 years after treatment. A different analysis confirmed that symptoms more frequently reported were tingling in toes and feet (30%), numbness in toes and feet (19%), tingling hands or fingers (15%), and burning or shooting pain in toes or feet (13%).[42] Dose-intensity was not associated with a worse neurologic outcome, although it was related to the oxaliplatin cumulative dose, and this association also occurred for trouble in standing or walking.

Improvement in surgery and the use of multimodal therapies in patients with ovarian cancer has allowed clinicians to achieve a 5-year survival rate of greater than 40% in this population.[43] In a study performed with a cohort of 116 patients with ovarian cancer, investigated at a median of 501 days after the end of treatment, 62% of the 100 responders reported the presence of peripheral neuropathy (according to EORTC questionnaires), and 29% defined them as significant intensity.[44]

EFFECT OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROTOXICITY ON THE QUALITY OF LIFE OF CANCER SURVIVORS

The number of cancer survivors and of patients in whom cancer has become a chronic disease is increasing in Western countries, and these people strongly require considerations about the effect of long-term toxicities on QoL. From this perspective, CIPN is likely to be one of the main survivorship issue.

However, only a few well-conducted analyses have been performed to quantify the real extent of the problem, and different methodological approaches have been used, which make a reliable comparison very difficult. Mols et al performed a systematic review of the available literature and found 11 studies that assessed the relationship that exists between CIPN and QoL.[45] Eight of these studies reported an association, whereas three failed to observe any association be-

tween CIPN and QoL. Because at least two of the three negative studies had substantial methodological flaws, the overall conclusion drawn from the review is that CIPN is very likely to be negatively associated with QoL in cancer survivors.

In a study that was not included in the previous review by Mols et al, Tofthagen et al investigated a cohort of patients treated with oxaliplatin up to 7 years after treatment and observed that 89% of them reported at least one symptom of neuropathy;[45,46] among these patients, 24% had difficulties in driving and 60% in exercising. All of the subscales of the short-form (SF)-36 were significantly associated with the presence and severity of CIPN, but no objective assessment of CIPN presence was included in the study design.

Another study was reported in 2014 by Ezendam et al,[47] who investigated a cohort of patients with ovarian cancer by using two EORTC QoL scales; the results demonstrated that CIPN symptoms were significantly associated with QoL impairment. However, because a quarter of the women who did not receive neurotoxic chemotherapy were affected by peripheral neuropathy symptoms, this result, in the absence of any objective evaluation, raises some concern about the validity of the selected assessment tool to really detect CIPN.

A specific and underestimated aspect of long-term CIPN is the possibility that neurologic impairment might cause an increased propensity to fall. This concern was raised originally by Tofthagen et al in 2012 in a small series of patients with cancer and CIPN; 20% of them had fallen recently.[48] An increased incidence of falls had already been reported in patients with cancer and in older populations.[49] Gewandter et al investigated a cohort of 471 patients with CIPN; 27% of participants reported functional impairment (e.g., difficulty in shopping or in doing common tasks necessary to live in their home independently), whereas 12% had a fall in the 3-month period preceding enrollment on the study.[50] When these results were analyzed in relation to the type of CIPN, motor neuropathy was significantly associated with falls, which suggests that, in the study cohort, taxanes used as breast cancer treatment were responsible for these events.[50]

HEALTH CARE PROVIDERS AND LONG-TERM CHEMOTHERAPY-INDUCED PERIPHERAL NEUROTOXICITY

The relationship existing between patients with cancer and their health-care providers is somewhat complex. Patients experience several different side effects, and an accurate discrimination of the contribution of CIPN to overall toxicity might be difficult. Moreover, patients often are worried by the possibility that effective treatment could be modified because of side effects. A study of 1,425 patients with cancer who had different malignancies demonstrated that patients often underreported their symptoms to health-care providers;[51] when a comparison was performed between the hospital notes and the patient interviews, the data did not correspond for the majority of the patients.[44] With specific reference to CIPN, moderate/severe symptoms were re-

ported by 29% of patients, whereas symptoms of any severity were reported by only 12% of patients according to the hospital notes that referred to follow-up visits. Conversely, health-care providers sometimes are insufficiently educated and trained to recognize the earliest evidence of CIPN. Moreover, with reference to this specific aspect, the possibility that long-term CIPN might be managed by primary care physicians and not only by oncologists should be considered. A survey fielded in 2009 and recently published revealed that long-term CIPN induced by paclitaxel was recognized by only 27% of primary care physician and the percentage was even lower (22%) for oxaliplatin-treated cancer survivors.[52] These results are not surprising, because no specific education and training are provided outside the oncology and neurology fields to recognize CIPN. However, with the aging population, cancer (and treatment-related toxicities) in the primary care setting are very likely to increase in the future.

Recent studies report a desire among patients for better information and support related to long-term/persistent treatment-related toxicities as well as greater awareness of these side effects among health care providers.[53]

CONCLUSION

The cure of cancer frequently is based on complex, hazardous, and toxic treatments, which are accepted because of their potential life-saving effects. However, cancer survivors deserve and ask for the best possible quality of survival after cancer treatment, particularly over the long term. Unfortunately, in several instances, this need is still unmet. Among the reasons for this situation, the insufficient knowledge of the pathogenesis of cancer treatment–related neurotoxicity is definitely one of the most important issues.

To achieve a better understanding of chemotherapy-induced neurotoxicity, accurate preclinical studies might provide very useful suggestions, but the translation of their results into the clinical setting is sometimes difficult. On the clinical side, a very important contribution to better knowledge of cancer treatment–related neurotoxicity could come from a more homogeneous, reliable, and systematic collection of the clinical data of treated patients. This will highlight similarities and differences between treatments to identify early predictors and to clarify individual susceptibilities to neurotoxicity that might represent invaluable clues to drive research into the proper direction and, eventually, provide reliable guidelines to manage CIPN.

The final aim of these investigations is to offer patients with cancer the possibility to be treated with affordable neurotoxicity or, at least, to provide them effective treatments. To this aim, a virtuous alliance among patients and treating physicians is needed. In fact, physicians should be trained not only at the use of treatments but also at the recognition and proper assessment of the first signs of neurotoxicity, and patients should be made aware of it to report early symptoms with the common goal of preventing irreversible damage.

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Challenges to Standardizing the Care for Adult Cancer Survivors: Highlighting ASCO's Fatigue and Anxiety and Depression Guidelines

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OVERVIEW

There are over 14 million survivors of cancer living in the United States alone and tens of millions more worldwide, with this population expected to nearly double in the next decade. The successes of prevention, early detection, and better therapies have lead to an emerging understanding of the substantial medical and psychosocial issues for this growing population that must be tackled for individuals and from the health care system and societal perspectives.

There are over 14 million survivors of cancer living in the United States alone and tens of millions more worldwide, with this population expected to nearly double in the next decade. The successes of prevention, early detection, and better therapies have lead to an emerging understanding of the substantial medical and psychosocial issues for this growing population that must be tackled for individuals and from the health care system and societal perspectives.

The major components of survivorship care include (1) surveillance for recurrence and new primary cancers, including consideration of genetic risk predisposition; (2) prevention, monitoring for, and management of long-term and late effects of cancer and cancer treatment, including medical and psychosocial issues; (3) counseling and assistance for optimizing health behaviors; and (4) coordination of care to assure that patients receive the appropriate evidence-based follow-up care from the appropriate provider at the right times.[2,3] Increasing awareness and delivery of this care in a patient-centered, proactive manner in our already overburdened health system has proven to be quite a challenge. This is, in part, because standardizing the care for survivors of cancer poses unique and substantial hurdles. Although individual patients have varying and diverse needs in all medical settings, cancer comprises myriad diseases necessitating a wide range of therapeutic interventions and associated risks in follow-up with diverse recommendations for care. Tailored proactive survivorship care planning is one potential solution to this issue, yet the resources, efforts, changes in standard conventions of care required, and the limited data demonstrating their value have limited their uptake to date.[4-6]

Another major and related issue is that cancer research to date has predominantly focused on improving disease control and cure rates. Relatively little dedicated research has centered on survivorship concerns. And much of the available data to inform the care of survivors has been observational from therapeutic clinical trials without patient-reported outcomes or from large databases with little granularity. Further, there have been few prospective studies, limited intervention research, and even fewer randomized trials of interventions to improve care and outcomes for survivors. Thus, the sparse evidence base to guide the care of survivors has generally led to heterogeneous follow-up and care concerning most issues for cancer survivors. And even in the few settings where enough data exists to inform evidence-based, systematic guidelines, they are not routinely followed.[7]

Finally, survivorship care in its infancy has suffered from a prior lack of prioritization.[8] Just like the treatment of most cancers, a one size fits all approach does not work for cancer survivorship care. Most recently, risk-based care has been advocated for targeting the appropriate care to individual patients, from the appropriate provider, at the most optimal times in the cancer care trajectory.[9] To address these needs, researchers, clinicians, and advocates worldwide have been working to define cancer survivors' needs and determine how to optimally deliver the care to meet them. Formalized in 2011, the American Society of Clinical Oncology's (ASCO's) Survivorship Committee aims to deliver high-quality survivorship care to enhance patients' long-term health by managing concerns related to cancer treatment and survivorship.[10] The committee offers educational opportunities and clinical guidance on survivorship care, including an array of guidelines focused on specific survivorship concerns,

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including anxiety, depression, and fatigue. In addition to this growing body of guidelines, the ASCO Cancer Survivorship Compendium is a repository of tools and resources to enable oncology providers to implement or improve survivorship care within their practices. This manuscript highlights two of the first guidelines that have emerged from the dedicated work of ASCO's Survivorship and Clinical Practice Guidelines Committees, surrounding fatigue, anxiety, and depression as targetable, treatable symptoms that are highly prevalent in cancer survivors.

CANCER-RELATED FATIGUE GUIDELINES

Fatigue is one of the most common and distressing symptoms of people undergoing cancer treatment.[11] In addition to fatigue during treatment, approximately one-third of patients will go on to experience persistent fatigue for months or years following the completion of their treatment.[12] As part of a larger effort to address symptom management and quality-of-life issues in post-treatment cancer survivors, ASCO's Cancer Survivorship Committee organized an expert panel charged with formulating a new clinical practice guideline or endorsing or adapting an existing guideline for screening, assessment, and management of post-treatment fatigue in survivors of adult-onset cancers.

The panel began by searching literature to determine whether guidelines existed that it could endorse or adapt. Based on the search and prespecified evaluation criteria,[13] the panel chose to adapt a 2011 pan-Canadian practice guideline for screening, assessment, and care of cancer-related fatigue.[14] This guideline was also informed by recommendations from the Oncology Nursing Society (ONS) and the National Comprehensive Cancer Network (NCCN).[15,16] The panel also considered two NCCN guidelines that had been created or updated since 2009.[17,18] The resulting adapted guideline was published in the *Journal of Clinical Oncology* in 2014.[13] The ASCO-adapted guideline is organized into an algorithm that specifies recommendations for screening, comprehensive and focused assessment, laboratory evaluation, treatment care options, and ongoing monitoring and follow-up.

KEY POINTS

- Standardizing survivorship care poses unique challenges.
- Increased awareness and prioritization of survivors' issues is necessary.
- A growing array of recommendations and tools are becoming available to improve survivorship care.
- Fatigue is a common effect that should be screened for and managed.
- Routine anxiety and depression screening in cancer survivors should lead to improved psychosocial outcomes.

Overview of the Clinical Algorithm for Cancer-Related Fatigue

Screening. The primary recommendations for screening are to screen all patients for fatigue at their initial visit, at appropriate intervals during and following treatment, and as clinically indicated; and to screen using brief self-report measures with established cutoff scores. One recommended way to screen is through use of a simple 0-to-10 numeric rating scale (0, no fatigue; 10, worst fatigue imaginable), where mild fatigue is indicated by scores of 1 to 3, moderate fatigue is indicated by scores of 4 to 6, and severe fatigue is indicated by scores of 7 to 10. The guideline further recommends that patients who report moderate to severe fatigue undergo a comprehensive and focused assessment.

Comprehensive and focused assessment. The primary recommendations for comprehensive and focused assessment are to conduct a focused fatigue history that evaluates the various features of the patient's experience of fatigue (e.g., associated or alleviating factors); to consider the possibility of disease recurrence; and, in the absence of disease recurrence, to assess treatable factors that may be contributing to fatigue (e.g., comorbidities, medications, nutritional issues). When conducting this assessment, the primary clinical team must decide when referral to an appropriately trained professional (e.g., cardiologist) is needed. Laboratory evaluations may also play a role in a comprehensive and focused assessment based on the presence of other symptoms and the onset and severity of fatigue. Possible laboratory evaluations include a complete blood cell count with differential and a comprehensive metabolic panel.

Treatment and care options. Regardless of the reported level of fatigue, the guideline recommends that all patients be offered education about fatigue after treatment (e.g., information about the difference between fatigue that is normal in most individuals following exertion or lack of sleep and cancer-related fatigue) and advice about general strategies to help manage fatigue (e.g., self-monitoring of fatigue). These issues may be further confounded in our aging population, including patients with cancer, and therefore cancer survivors as well. For patients reporting moderate or severe fatigue, the guideline first recommends treating contributing factors identified as part of the comprehensive and focused assessment. For example, the assessment may suggest that the patient's fatigue can be addressed by treating their sleep problem or pain problem. Beyond this action, the guideline indicates that patients with moderate to severe fatigue may benefit from physical activity, psychosocial, mind-body, or pharmacologic interventions. At present, there are no clear standards for selecting among these interventions to treat an individual patient, and research is needed about how best to prioritize, sequence, and link the available treatment options. The guideline contains specific recommendations for each type of intervention based on a review of existing guidelines and a re-

cent literature review. Readers may also wish to review a recent ONS update on evidence-based interventions for cancer-related fatigue.[19]

Ongoing monitoring and follow-up. For patients who received treatment for fatigue, the guideline recommends that they be observed and re-evaluated regularly to determine whether treatment has been effective or needs to be readdressed. For patients who did not receive treatment for fatigue, the guideline recommends promotion of ongoing self-monitoring and screening at follow-up visits since fatigue can still emerge as a late effect.

Challenges and Opportunities for Implementing the Cancer-Related Fatigue Guideline

Many of the challenges in implementing this guideline will be similar to those identified for the broader challenge of implementing survivorship care plans. One important issue is the significant time and resources required to develop care plans.[10] Proposed solutions for this problem included development of automated, programmable applications to expedite the process.[10] Another important issue is health care providers' concern that they possess insufficient knowledge of cancer survivor issues to adequately address them.[20] Efforts to address this issue should include dissemination of the guideline and related information in formats and forums desired by providers. With regard to the current guideline, ASCO University recently posted a brief web-based educational program summarizing the recommendations.[21] Other challenges more specific to fatigue include the lack of documentation about fatigue levels and the lack of supportive care referrals for providing interventions for fatigue. Documentation can potentially be improved by introducing routine symptom screening using electronic methods (e.g., computer kiosks or tablets) that deliver the information collected immediately to clinicians for review and action.[22] Finally, referrals can be facilitated by identifying in-house or community resources that can provide relevant interventions. Also, it may be possible to deliver certain interventions to patients remotely via the Internet.[23]

ANXIETY AND DEPRESSION GUIDELINES

ASCO provided practice recommendations adapted from the Pan-Canadian guideline on Screening, Assessment, and Care of Psychosocial Distress (Depression, Anxiety) in Adults with Cancer,[24] which addressed the optimum screening, assessment, and psychosocial-supportive care interventions for adults with cancer who are identified as experiencing symptoms of depression and/or anxiety.

The ASCO panel underscores that health care practitioners implementing the guideline recommendations should first identify the available resources in their institution and community for the treatment of anxiety and depressive anxiety

symptoms. The availability and accessibility of supportive care services for all are important in preventing or reducing the severity of symptoms of psychopathology. As a minimum, practitioners should verify with their institution or local hospital the preferred pathway for care of an individual who may present with a psychologic or psychiatric emergency. Presented first are the recommendations applicable to both anxiety and depressive symptom presentations, followed by the considerations unique to each.

General Recommendations

Screening. All patients should be screened for psychologic symptoms at their initial visit, at appropriate intervals, and as clinically indicated, especially with changes in disease status (e.g., post-treatment, recurrence, progression) and when there is a transition to palliative and end-of-life care. Screening should be done using valid and reliable measures of anxiety or depressive symptoms that feature reportable scores (dimensions) that are clinically meaningful (established cutoffs). A phased screening and assessment that does not rely simply on a symptom count from the screening measure is recommended. Consider the need to use culturally sensitive measures. Tailor further assessment or treatment for those with learning disabilities or cognitive impairments.

Identification or determination of the presence or absence of pertinent history or risk factors is important for interpretation of the screen and decision making for subsequent follow-up assessment. Other concerns that may become evident with screening, such as risk of harm to self and/or others, severe anxiety or agitation, or the presence of psychosis or confusion (delirium) requires referral to a psychiatrist, psychologist, physician, or equivalently trained professional for emergency evaluation. Facilitate a safe environment and one-to-one observation, and initiate appropriate harm-reduction interventions to reduce risk of harm to self and/or others.

Follow-up assessment. When moderate-to-severe or severe symptomatology is detected through screening, individuals should have a diagnostic assessment to identify the nature and extent of the symptoms and the presence or absence of anxiety disorder(s) or mood disorders. The clinical team must decide when referral to a psychiatrist, psychologist, or equivalently trained professional is needed for diagnostic assessment. The clinical team should share responsibility for assessments, designating those who are expected to conduct assessments as per scope of practice. If a patient needs a referral for the treatment of anxiety or depression, discuss with the patient the reason(s) for and anticipated benefits from the referral. Further, the clinical team should subsequently determine the patient's compliance with the referral.

Treatment. Medical (e.g., unrelieved symptoms such as pain and fatigue, or delirium brought on by infection or electrolyte imbalance) or substance abuse causes of anxiety or

depression should be treated first. Offer support and provide education and information about anxiety or depression and its management to all patients and their families, and explain the specific symptoms or symptom worsening that warrant a call to the physician or nurse.

Psychologic and psychosocial interventions should derive from relevant treatment manuals of empirically supported treatments specifying the content and guiding the structure, delivery mode, and duration. Use of treatment outcome measures should be routine (minimally pre- and post-treatment) to (1) gauge the efficacy of treatment for the individual patient, (2) monitor treatment adherence, and (3) evaluate practitioner competence.

Special Considerations: Depressive Symptoms and Mood Disorders

Screening for symptoms. The Patient Health Questionnaire-9 (PHQ-9) is recommended for depression screening. The first two items assess for the classic symptoms of low mood and anhedonia. If a patient endorses either item (or both) as occurring for more than half of the time or nearly every day within the past 2 weeks (i.e., a score of ≥ 2), he or she should complete the remaining items of the PHQ-9.[25,26] It is estimated that 25% to 30% of patients would need to complete the remaining items. The traditional cutoff for the PHQ-9 is 10 or greater. The panel's recommended cutoff score of 8 or greater is based on study of the diagnostic accuracy of the PHQ-9 with cancer outpatients. A meta-analysis by Manea et al also supports the 8 or greater cutoff score.[27] As suggested for screening, it is important to determine the associated sociodemographic, psychiatric or health comorbidities, or social impairments, if any, and the duration that depressive symptoms have been present.

Follow-up assessment. If moderate-to-severe or severe symptomatology is detected, individuals should have a diagnostic assessment to identify the nature and extent of the depressive symptoms and the presence or absence of a mood disorder. The assessment should also identify the severity of cancer symptoms (e.g., fatigue), possible stressors, and risk factors for depression.

Treatment for mood disorders. It is recommended to use a stepped care model and tailor intervention recommendations based on variables such as the following:
- Current symptomatology level and presence or absence of *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) diagnosis.
- Level of functional impairment in major life areas.
- Presence or absence of risk factors.
- History of and response to previous treatments for depression.
- Patient preference.
- Persistence of symptoms following receipt of an initial course of depression treatment.

For severe levels of depressive symptoms or a diagnosed mood disorder, use pharmacologic, psychologic (e.g., psychotherapy, psychoeducational therapy, cognitive-behavioral therapy, and exercise) or combined treatment delivered by appropriately trained individuals.[28-38] Depressive disorders have special characteristics.[34,35] Many individuals (50% to 60%) with a diagnosed depressive disorder will have a comorbid anxiety disorder, with generalized anxiety being the most prevalent.[39] If an individual has comorbid anxiety symptoms or disorder(s), the route is usually to treat the depression first. Also, some people have depression that does not respond to an initial course of treatment.

Follow-up and reassessment. Persons with depressive symptoms commonly lack the motivation necessary to follow through on referrals and/or to comply with treatment recommendations. With this in mind, on a biweekly or monthly basis until symptoms have remitted, consider the following:
- Assess follow through and compliance with individual or group psychologic or psychosocial referrals, as well as satisfaction with these services.
- Assess compliance with any pharmacologic treatment, patient concerns about side effects, and satisfaction with the treatment's symptom relief.
- If compliance is poor, assess and construct a plan to circumvent obstacles to compliance or discuss alternative interventions that present fewer obstacles.
- After 8 weeks of treatment, if symptom reduction and satisfaction with treatment are poor despite good compliance, alter the treatment course (e.g., add a pharmacologic intervention to a psychologic, change the specific medication, refer to individual psychotherapy if group therapy has not proved helpful).[34,35,40]

Special Considerations: Anxiety Symptoms and Disorders

Screening for symptoms. Anxiety disorders include specific phobias and social phobia, panic and agoraphobia, generalized anxiety disorder (GAD), obsessive compulsive disorder, and post-traumatic stress disorder. It is recommended that patients be assessed for generalized anxiety disorder, as it is the most prevalent of all anxiety disorders and commonly comorbid with others, primarily mood disorders or other anxiety disorders (e.g., social anxiety disorder).[39]

The GAD-7 scale is also recommended. Patients with GAD do not necessarily present with symptoms of anxiety. The pathognomonic GAD symptom—multiple excessive worries—may present as concerns or fears. Whereas cancer worries may be common for many, GAD worry or fear may be disproportionate to actual cancer-related risk (e.g., excessive fear of recurrence, worry about multiple symptoms, or symptoms not associated with current disease or treatments). Importantly, an individual with GAD has

worries about a range of other noncancer topics and areas of his or her life.

Follow-up assessment. The assessment should identify signs and symptoms of anxiety (e.g., panic attacks, trembling, sweating, tachypnea, tachycardia, palpitations, sweaty palms), severity of symptoms, possible stressors (e.g., impaired daily living), risk factors, and times of vulnerability and should also explore underlying problems or causes. If a patient has severe symptoms of anxiety following the further assessment, when possible, confirm an anxiety disorder diagnosis before initiating any treatment options (e.g., DSM-5, which may require making a referral).

Treatment for anxiety disorders. For a patient with moderate anxiety, the primary oncology team may choose to manage the concerns using typical supportive care management. In addition, the team can use a stepped care model to tailor any additional intervention recommendations based on variables such as the following:

- Current symptomatology level and presence or absence of DSM-5 diagnoses.
- Level of functional impairment in major life areas.
- Presence or absence of risk factors.
- Chronicity of GAD and response to previous treatments, if any.
- Patient preference.

If anxiolytic therapy is used, patients should be informed of the side effect profiles of the medications, tolerability of treatment (including the potential for interaction with other current medications), response to prior treatment, and patient preference. Patients should be warned of any potential harm or adverse effects—particularly about the long-term use of benzodiazepines in the treatment of anxiety. These medications carry an increased risk of abuse and dependence and are associated with side effects including cognitive impairment. As a consequence, use of these medications should be time limited in accordance with established psychiatric guidelines.[41]

Follow-up and reassessment. Because cautiousness and a tendency to avoid threatening stimuli are cardinal features of anxiety pathology, persons with symptoms of anxiety commonly do not follow through on referrals or treatment recommendations. With this in mind, the mental health professional or other member of the clinical team managing the patient's anxiety should assess the following on a monthly basis or until symptoms have subsided:

- Follow through and compliance with individual or group psychologic or psychosocial referrals, as well as satisfaction with the treatment.
- Compliance with and pharmacologic treatment, patient's concerns about side effects, and satisfaction with the symptom relief provided by the treatment.[2,34,42]

If medications are used, consider tapering if symptoms are under control and if the primary environmental sources of anxiety are no longer present. Longer periods of tapering are often necessary with benzodiazepines, particularly with potent or rapidly eliminated medications.

If compliance is poor, assess and construct a plan to circumvent obstacles to compliance, or discuss alternative interventions that present fewer obstacles. After 8 weeks of treatment, if symptom reduction and satisfaction with treatment are poor despite good compliance, alter the treatment course.

SUMMARY OF ANXIETY AND DEPRESSION GUIDELINES

As noted in the 2008 Institute of Medicine report, *Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs*, and confirmed in a recent report,[43] the psychologic needs of patients with cancer are not being addressed, posing a serious problem for U.S. health care. If psychologic needs are not addressed, regardless of when they arise, they then predict later stress and anxiety,[44,45] depressive symptoms,[46] low quality of life,[47] and increased side effects with treatment and more physical symptoms.[48-51] Alternatively, treatment for either anxiety or depression can successfully address issues such as these[31,52] and has the potential to reduce the risk of recurrence[53] or cancer death.[48-50,54]

Overall, mood disorders are associated with lower quality of life and soaring health care costs.[55,56] Patients with cancer who are depressed worry about their disease (70%), relationships with friends (77%), the well-being of family members (74%), and finances (63%),[57] and the sequelae of this includes more symptom distress[58-60] and maladaptive coping,[61] among others. Depression in particular is associated with heightened risk for premature mortality (recurrence risk = 1.22–1.39) and cancer death (recurrence risk = 1.18).[50,62] Two studies have now documented increased rates of suicide among populations of long-term survivors of breast and testicular cancer.[63,64]

Anxiety is the most common mental health issue for long-term cancer survivors.[65] Heightened anxiety is associated with increased side effects and symptoms[66] and poorer physical functioning.[67] Worry, the hallmark of GAD, can be multifocal[68] with content shifting over time from treatment concerns to physical symptoms and limitations.[69] Be it stress, anxiety, or worry, all are related to important neuroendocrine changes,[70] which may account, in part, for the poorer survival among patients with cancer who have heightened stress.[71]

The majority of patients with cancer do well, manifesting remarkable resilience at diagnosis, treatment, and thereafter. Regardless of the timing and circumstances by which any psychiatric comorbidity may arise, patients can experience enormous emotional, interpersonal, and financial costs, and providers and the health care system alike can encounter economic consequences when depressive and anxiety disorders are not treated. Screening and early, efficacious treatment for those manifesting significant symptoms of anxiety or depression holds the potential to reduce the human cost of cancer, not only for patients and survivors but also for those who care for and about them.

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PATIENT AND SURVIVOR CARE

Managing Side Effects of Endocrine Therapy in Men and Women

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Sexual Healing in Patients with Prostate Cancer on Hormone Therapy

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OVERVIEW

Since prostate cancer becomes more common with age, at least one-third of men have sexual problems at diagnosis. All localized treatments for prostate cancer greatly increase the prevalence of sexual dysfunction, which include loss of desire, erectile dysfunction, and changes in orgasm. Even men on active surveillance have a higher rate of problems than matched peers without prostate cancer. However, men given androgen deprivation therapy (ADT) have the worst rates of sexual dysfunction. Even after 3 to 4 months of ADT, men's desire for sex is decreased and irreversible damage may occur to the erectile tissue in the penis. Erections do not recover in about one-half of men, even if ADT is discontinued. Although intermittent ADT allows some recovery of sexual function, serum testosterone requires 9 to 12 months off ADT to recover. Again, one-half of men have permanent erectile dysfunction. If ADT causes atrophy of the erectile tissue, blood leaks out of the venous system during erection. This syndrome is difficult to treat except with surgery to implant a penile prosthesis. Despite the high rate of sexual problems in men on ADT, a small group stays sexually active and is able to have reliable erections. To improve men's sexual satisfaction on ADT, it may be important to educate them about getting extra mental and physical sexual stimulation, as well as using penile rehabilitation during hormone therapy. Information on reaching orgasm and coping with problems such as dry orgasm, pain with orgasm, and urinary incontinence during sex also should be provided.

In 1998 I spoke about sexuality for men with prostate cancer and their partners at a large symposium at the University of Michigan. Only about 5 minutes of my 25-minute talk was devoted to sexual function and androgen deprivation therapy. I acknowledged that most men noticed a decrease in their desire for sex, had difficulty getting and keeping erections, and required more effort to reach an orgasm. However, I pointed out that as many as 20% of men had satisfying sex with a partner at times, although it took more mental and physical stimulation to get aroused and have an orgasm. Men with erection problems also might still enjoy sex enough to get medical or surgical treatment to improve their erections. The next day, a woman told me how important my presentation was to her and her husband. During his 3 years on hormone therapy, they never had sex. His oncologist said it would not be possible. My talk inspired them to go back to the hotel and try. The result was a very satisfying session of lovemaking that included intercourse with a firm erection and orgasms for both partners.

Such instant cures have not been common during my career, but this incident highlights the importance of providing men and their partners more optimistic, though accurate, expectations about sexuality during hormone therapy. Our culture tends to believe that hormones have absolute power to control sexual desire and function instead of seeing them as one factor in the complex interaction of sexual beliefs and experiences, relationship issues, and skills in coping with a chronic illness.

This article summarizes what is known about men's sexual function during androgen deprivation therapy for prostate cancer and suggests options to help men and their partners maintain more active sex lives if desired.

SEXUAL FUNCTION IN MEN WITH PROSTATE CANCER

One-third to one-half of men already have sexual dysfunction at the time of prostate cancer diagnosis. Prevalence increases with aging and comorbid disease.[1-3] In addition, all current treatments for localized prostate cancer, including active surveillance, greatly increase rates of sexual dysfunction. Men randomly assigned to active surveillance or radical prostatectomy in the Scandinavian Prostate Cancer Group Study were compared to matched controls.[4] At 12-year follow-up, 84% of men who had a prostatectomy, and 80% of men on active surveillance, but only 43% of controls had erectile dysfunction (ED). Although 28% of men on surveillance began androgen deprivation therapy (ADT) in the interim, and others had progressive disease, ED may increase with damage to the neurovascular bundles from repeated

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prostate biopsies.[5] Similarly, ED rates a year after diagnosis of localized prostate cancer in 771 Norwegian men were 76% in those on surveillance, 89% after radical prostatectomy, 83% after radiotherapy, and 84% after combined radiotherapy and hormone therapy.[6]

Sexual and urinary function in men diagnosed with prostate cancer were significantly worse than in healthy controls in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial in the United States (p < 0.001).[7,8] Side effects persisted across 10 years of follow-up. More than 95% of men in each cancer treatment group reported sexual dysfunction and 50% had urinary or bowel dysfunction. Diagnosis by prostate-specific antigen (PSA) screening theoretically could downstage the cancer, but screening reduced neither long-term mortality nor rates of sexual, urinary, or bowel complications.

ANDROGEN DEPRIVATION FOR PROSTATE CANCER AND ITS EFFECT ON SEXUAL FUNCTION

Androgen deprivation therapy has been used in a variety of ways to treat patients with prostate cancer over the past 70 years, ever since the discovery that signaling from androgen receptors in prostate cancer cells is responsible for at least some of the proliferation and recurrence of disease.[9] However, even when ADT succeeds in controlling cancer cells that are sensitive to hormones, cancer progression may take place because of clones of cells that are less dependent on androgens. Second-line hormone treatment with drugs such as abiraterone or the androgen blocker enzalutamide also has been shown to be beneficial even when first-line ADT has failed.[9]

Androgen deprivation therapy, whether with bilateral orchiectomy, luteinizing hormone-releasing hormone agonists or antagonists, helps treat prostate cancer symptoms in men

KEY POINTS

- Men with prostate cancer have a high prevalence of sexual dysfunction because of age, comorbidities, and damage from definitive treatment for localized disease.
- Androgen deprivation therapy adds to the problem because of the loss of hormone stimulation in the brain and direct damage to the erectile tissue.
- Men who have good sexual function at the time of prostate cancer diagnosis and who are in a sexual relationship with a partner who wants to stay active are more bothered by the sexual dysfunction.
- Preventing and treating problems may involve counseling the man or couple on how to achieve more intense sexual stimulation, how to improve sexual communication and avoid performance anxiety, and how to decide whether to try a treatment to restore better erections.
- Men who have sex with men have some special issues, including a greater emphasis on the sensual qualities of semen at ejaculation and sometimes a need for a more rigid erection to allow anal penetration.

with metastatic disease and may prolong survival,[10] but it also increases the risks of cardiovascular disease, osteoporosis, and sexual dysfunction.[10] It remains unclear if using ADT as neoadjuvant treatment before radical prostatectomy prevents recurrence in men with high-risk disease, although benefits in survival have been demonstrated from combining ADT with external beam radiation therapy in this patient subgroup.[10] It has become increasingly clear, however, that ADT as a monotherapy is inferior to active surveillance in older men with organ-confined prostate cancer, causing morbidity but not prolonging survival.[11,12]

Rates of sexual problems are high among men on ADT. These problems include a decreased desire for sex, difficulty getting and keeping erections, reduced semen volume, trouble reaching orgasm, and distress about gynecomastia and feminization of fat distribution.[13] Many men surveyed already had definitive local treatment with radical prostatectomy or radiation therapy. Their sexual function was severely damaged before the onset of ADT, making it difficult to attribute additional problems to hormone therapy.[4,6,8,14-16] Nevertheless, sexual function is poorer in men who had past or current ADT when compared to men only treated with surgery or radiation therapy.[17-19] Even after 3 or 4 months of ADT, damage to erectile function is likely to be permanent because of alterations to the smooth muscle in the cavernous bodies of the penis. During erection, despite adequate arterial inflow of blood, the veins draining blood from the erectile tissue are not occluded and penile rigidity cannot be maintained.[19] ADT also impairs nocturnal erections, which may be important sources of oxygenated blood to the penis after localized prostate cancer treatment by helping nerves to heal and maintaining the health of endothelial cells in the erectile tissue.

Men who rate their degree of distress or "bother" about sexual dysfunction as greater also report more depression and poorer quality of life.[16] Not surprisingly, men are more bothered by sexual problems if they are younger and have better sexual function when diagnosed with prostate cancer or starting ADT, and if their relationship is more satisfying (i.e., they have more to lose).[2,3,16] Distress about sexual problems also is associated with more caregiving stress and poorer quality of life in the spouses of men diagnosed 3 years previously with prostate cancer.[20]

Some men are given double-blockade therapy by adding an androgen blocker to ADT. Although survival benefits of double blockade are dubious,[10,21] drugs such as finasteride or bicalutamide may directly damage the smooth muscle inside the cavernous bodies, increasing the risk of venous leak and irreversible erectile dysfunction.[22]

INTERMITTENT ANDROGEN DEPRIVATION THERAPY

Another issue is whether intermittent hormone therapy is as effective as continuous ADT in prolonging survival while maintaining better quality of life, including recovery of sexual function during time off ADT.[23] Two recent, large phase III trials suggest that intermittent ADT is equivalent to con-

tinuous ADT in prolonging survival in men who have a rising PSA after definitive treatment for local disease, while allowing somewhat better quality of life.[22] In men with metastatic disease, mean survival was slightly longer (5.8 vs. 5.1 years) when continuous ADT was used, but the clinical significance of the results is not very convincing.[23]

Men often remain profoundly hypogonadal for months after ADT is withdrawn, especially if they are older or have had several cycles on and off ADT.[22] Not surprisingly, recovery of quality of life, including sexual function, is correlated with serum testosterone levels. Typically, about one-half of men recover better erections when off ADT, but only a minority remains sexually active after several months. The rate of sexual inactivity may be even greater for men who have metastatic disease.[24] The structural changes in the erectile tissue of the penis related to ADT or androgen-blocking drugs may contribute to men's discouragement about sexual function. Continuing impairment of sexual desire and arousability related to central nervous system effects undoubtedly also play a role.[25]

One of the largest prospective trials to measure sexual function during intermittent ADT was a phase II cohort study of 250 men treated with a combination of flutamide and leuprolide for 9 months, with subsequent times off treatment over 2 years if the PSA was 4 ng/mL or less.[26] About one-half had biochemic recurrence after definitive localized treatment; others had locally advanced or metastatic disease at diagnosis. As expected, sexual function already was impaired at baseline, with 57% reporting erection problems, 47% low desire, and 46% sexual inactivity. All self-report measures deteriorated over the 9 months of ADT and only 13% remained sexually active. During their time off ADT, 52% of men sexually active at baseline resumed sex and all reported improved erectile function. However, 9 to 12 months off ADT was necessary to reach optimal recovery. Although desire for sex and feeling masculine improved during time off ADT, these outcomes remained poorer than at baseline. Approximately 15% of men who continued having sex during ADT reported adequate erections. The authors did not report factors that may identify the subgroup of men who maintain fairly normal sex lives during ADT, but the author's clinical experience suggests that younger age, a strong desire for sex at prostate cancer diagnosis, and being in a relationship with good sexual communication are all good prognostic factors.

INTERVENTIONS TO MAINTAIN SEXUAL SATISFACTION IN MEN ON ANDROGEN DEPRIVATION THERAPY

As the anecdote at the beginning of this article suggests, an important factor in helping men maintain sexual activity and satisfaction during ADT is to provide positive, although realistic, expectations. Not all men or their partners have a strong desire to stay sexually active, especially if ADT that began after definitive therapy for localized disease already impaired erections.

For those who want a sex life, I often cite a classic study demonstrating that hypogonadal men have more trouble than men with normal hormone levels in getting subjectively aroused or achieving erections if they are asked to generate their own sexual fantasy.[27] However, when shown an erotic film, their arousal and erections are similar to those of eugonadal men. Thus, it is likely to take both extra physical caressing and mental sexual stimulation for a man to experience arousal or to get the best possible erection when on ADT. I counsel men and their partners to put a priority on time for intimate touching, rather than waiting for spontaneous desire. A sensate focus framework helps partners regard sexual caressing as a time to share intimacy rather than an occasion to demonstrate sexual performance.[28]

Men who begin with good erectile function may benefit from penile rehabilitation using medical treatments for erectile dysfunction, such as oral medication, vacuum erection devices, or penile injections several times a week to ensure a regular supply of oxygenated blood to the erectile tissue.[29] The utility of penile rehabilitation during ADT has not been studied yet in a randomized trial.

Some men are not able to maintain firm erections even if they want to be sexually active, and can get subjectively aroused, because of damage to the smooth muscle and venous occlusion mechanism in the erectile tissue. This erection problem is unlikely to be treated successfully with oral, phosphodiesterase-5 inhibitors, a vacuum erection device, or penile injection therapy. It may require surgery to implant an inflatable penile prosthesis.[30] Motivation to have surgery is often related to the importance sexuality is in a man's life and his current relationships status. Men who have sex with men may need a more rigid erection to achieve anal penetration, which also could make a penile prosthesis attractive.[31] Some men switch from preferring to be the partner who penetrates anally to being the anal receptive partner as a way to get sexual pleasure despite erectile dysfunction.

With or without firm and reliable erections, men can still experience the sensation of orgasm during or after ADT, but it may require more intense sexual stimulation over a longer period of time than before. For partners, the effort to help a man reach orgasm can turn sex from a pleasurable sharing of intimacy into a work session. I often encourage couples to incorporate vibrator stimulation into their sexual caressing. A vibrator provides a different and intense type of sexual pleasure with less effort than prolonged manual or oral stimulation of the penis. For men who enjoy vaginal or anal penetration, vibrators that mimic the sensation are available. Other options include the Viberect, a medical-grade vibrator that can vary the frequency and intensity of stimulation, or high-tech vibrators that provide a range of types of physical sensations. If partners are open to watching erotic videos during sex, the extra mental stimulation may help a man to get as aroused as possible. If the couple finds that the use of erotic films has a negative effect on their intimacy, the man can watch a video just before starting sexual activity with a partner.

Since the prostate and seminal vesicles produce the liquid components of semen, men who have had radical prostatectomy have dry orgasms that include pleasurable sensations and muscle contractions, but without semen coming out of

the penis.[32] After external beam radiotherapy or brachytherapy, semen volume is often greatly reduced. Since dihydrotestosterone in the prostate regulates semen production, even men who begin ADT without prior definitive treatment of local prostate cancer usually have greatly reduced semen volume. Men often believe that women can feel semen spurting into the vagina during intercourse. In fact, most women do not miss having semen at ejaculation. Some women feel more comfortable giving a man oral stimulation if he has dry orgasms. In gay couples, however, loss of semen volume is more often viewed as making sex less sensual and enjoyable.[31] Other changes in orgasm after prostate cancer treatment may include less intensity and pleasure, pain at the moment of orgasm, or after radical prostatectomy, leaking urine during sexual arousal or orgasm.[32] Putting a tension ring at the base of the penis that occludes the urethra during sex can be helpful when leaking urine bothers a man or his partner.[33]

THE ROLE OF EXERCISE IN MAINTAINING SEXUAL SATISFACTION

The focus on energy balance in preventing prostate cancer and in promoting better quality of life after prostate cancer has led to randomized trials that add aerobic/strength training exercise for men starting ADT. Despite the well-documented morbidities of ADT on cardiovascular metabolism, fat distribution, and bone density, trials have often failed to prove a significant effect of exercise on quality of life in men on ADT.[34] A well-designed study that randomly assigned men to usual care versus exercise for 6 months after radical prostatectomy found improvements in physical fitness in the intervention group, but no impact on recovery of erectile function.[35] Recently a pilot study of only 57 men on ADT compared usual care to an exercise intervention group. The study found that the exercise group was significantly more likely to be sexually active after a 12-week program (p = 0.024).[36] However, only 21% of the exercise group men were sexually active at baseline compared to 17% at the end of the brief treatment. In the usual care group, rates of sexual activity were 22% at baseline and 0% post-treatment.

A review of the literature on prostate cancer and sexual function suggests that the best outcomes occur with multidisciplinary care that addresses physiologic damage to the sexual response as well as a man's coping skills and relationships.[28] If he is in a committed relationship, including the partner is also helpful.

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Bone Health in Adults Treated with Endocrine Therapy for Early Breast or Prostate Cancer

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OVERVIEW

Bone is a hormonally responsive organ. Sex hormones and calcium regulating hormones, including parathyroid hormone, 1–25 dihydroxy vitamin D, and calcitonin, have effects on bone resorption and bone deposition. These hormones affect both bone quality and bone quantity. The sex hormone estrogen inhibits bone resorption, and estrogen therapy has been developed to prevent and treat osteoporosis. Androgens are an important source of estrogen through the action of the enzyme aromatase and may themselves stimulate bone formation. Hence, the sex steroids play a role in bone metabolism. Breast cancer and prostate cancer are frequently hormonally responsive and may be treated with antiestrogens or antiandrogens respectfully. In addition, chemotherapy and supportive medications may alter the patient's endocrine system. In general, the suppression of sex hormones has a predictable affect on bone health, as seen by loss of bone mineral density and increased risk of fragility fractures. The bone toxicity of cancer-directed endocrine therapy can be mitigated through screening, counseling on optimization of calcium and vitamin D intake, exercise, and other lifestyle/behavioral actions, as well as the use of medications when the fracture risk is high. Maintaining bone health in patients who are treated with endocrine therapy for breast and prostate cancer is the focus of this review.

In the United States, approximately one in eight women will be affected by breast cancer and one in seven men will be affected by prostate cancer. Screening techniques and excellent therapies exist for both of these cancers. Although there remains room for improvement, the cure and survival rates for both of these cancers are high. It is estimated that there are more than 2.8 million breast cancer survivors and more than 2.7 million prostate cancer survivors alive today in the United States.[1,2] Breast cancer and prostate cancer are frequently hormonally responsive and may be treated with antiestrogens or antiandrogens. In general, the suppression of sex hormones during cancer therapy has a predictable affect on bone health, as seen by loss of bone mineral density and increased risk of fragility fractures. Hence, in terms of survivorship of these patients, long-term bone health issues, including osteoporosis, are a public health concern.

When treating breast and prostate cancer in the adjuvant setting, the goals of care are curative. For metastatic breast or prostate cancer, the goals of care are palliative. Metastatic breast and prostate cancers typically affect life expectancy and often cause bone metastases. Although the following discussion of bone health includes much that is applicable to both adjuvant and metastatic care, the focus is on the non-metastatic setting.

OSTEOPENIA AND OSTEOPOROSIS IN THE OLDER ADULT POPULATION

In the United States, approximately 10 million people have osteoporosis and an additional 43 million have low bone density.[3,4] Low bone mass correlates with an increased risk for fracture, and fractures are associated with substantial morbidity and mortality. Approximately one in two women and one in five men in the United States will experience an osteoporotic fracture.[3] A particularly disconcerting fact is that a hip fracture is associated with 8% to 36% excess mortality within 1 year. In addition, 20% of patients with a fracture of the hip require long-term nursing home care, and 60% will not regain their prefracture level of independence.[3] In addition to the pain and suffering associated with fractures, they are also is a substantial burden to health care expenditure.

A standard technique for measuring bone mineral density (BMD) is dual energy X-ray absorptiometry (DXA). The World Health Organization[5] has defined conditions of low bone mass using BMD as outlined in Table 1. The T score represents the standard deviation from an ideal bone mass. The BMD measurement provides the diagnostic criteria of osteoporosis as well as a threshold for pharmaceutical intervention.[4] Although the T score provides the operational definition of osteoporosis, the underlying health concern is the risk for fracture, not simply having a low DXA T score. There

TABLE 1. World Health Organization Diagnostic Thresholds for Low Bone Mass Using DXA Results for Men and Women[44,52,53]

	Interpretation of DXA Measurement	T Score
Normal	BMD more than 1 SD below the young adult female reference mean	≥ 1
Osteopenia	BMD more than 1 SD but less than 2.5 SD below the young adult mean	< 1 and > 2.5
Osteoporosis	BMD 2.5 SD or more below the young adult female mean	≤ 2.5
Severe Osteoporosis	BMD 2.5 SD or more below the young female adult mean in the presence of one or more fragility fractures	≤ 2.5 and clinical fragility fracture

Abbreviations: WHO, World Health Organization; DXA, dual energy x-ray absorptiometry; BMD, bone mineral density; SD, standard deviation.

is a movement by the National Bone Health Alliance to revise the working definition of osteoporosis such that it captures more than simply the DXA result and more fully reflects the risk of fracture.[6] Risk factors for fracture include increased age, low bone mass, prior fragility fracture, falls, impaired vision, low body weight, neuromuscular deficits, vitamin D deficiency, and a variety of medications.[7]

BONE HEALTH CARE FOR THE GENERAL POPULATION

Osteoporotic fractures are a public health concern and a wide range of free multilingual educational resources addressing bone health are publically available to address this issue. These high-quality, data-driven patient educational materials are available through the National Institutes of Health,[8]

Center for Disease Control,[9] Agency for Healthcare Research and Quality,[10] and other nongovernmental organizations such as the National Osteoporosis Foundation.[11] Similarly, numerous organizations, foundations, and government agencies have generated clinical practice guidelines on the management of bone health. Two selected guidelines on the recommendations for screening and treatment of bone health are summarized in Table 2.

BONE AS A HORMONALLY RESPONSIVE ORGAN

Bone is a dynamic organ and is constantly remodeling. Bone remodeling is the process of removal and replacement of bone mass at the same site. The remodeling process is critical to maintain mineral homeostasis and bone strength and to repair microdamage. The calcium level of extracellular fluid is tightly regulated through coordination of the gastrointestinal tract, kidneys, and bone. Systemic hormones that regulate these minerals are calcitonin, calcitriol (active vitamin D), and parathyroid hormone. Other critical systemic hormones for bone include growth hormone, insulin like growth factor, cortisol, estrogens, and androgens. These hormones play different roles throughout the life span of an individual as the skeleton changes with the aging process.[12,13]

The ratio of bone resorption to bone deposition fluctuates throughout life and is affected by steroid hormones. During youth the skeleton acquires bone mass, which reaches a plateau in young adulthood to middle age. In women, bone resorption accelerates at the onset of natural menopause and typically outpaces bone formation. During menopause, bone loss from the lumbar spine is 2 to 3% per year for approximately 5 years. Subsequently, the rate of bone loss is 0.5 to 1.0% per year, and is similar in both older men and women.[12,14] Deficiency of either estrogen or androgen promotes an increase in the number of osteoclasts and osteoclast activation, leading to an increased rate of bone resorption that outpaces bone formation.

ENDOCRINE THERAPIES AND BONE HEALTH

There is a possibility of low bone mass and/or fragility fractures as comorbid conditions at the time of cancer diagnosis and a pre-existing metabolic bone condition may influence the plan of care. Breast cancer and prostate cancer are frequently treated with adjuvant antiestrogens or antiandrogens respectively. These endocrine therapies can be considered risk factors for osteoporosis or fracture when assessing bone health in this patient population. If a fracture occurs in someone with a diagnosis of breast or prostate cancer, it is prudent to assess whether the fracture is pathologic in nature. Therapies for osteoporotic and pathologic fractures have many similarities, but there are also differences in treatment and fundamental differences in the goals of care.

Breast and Prostate Cancer Therapies That Increase the Risk of Bone Loss and Fracture

It has been known for many years that oophorectomy and orchiectomy can improve outcomes of patients with meta-

TABLE 2. Overview of Two Prominent Bone Health Screening and Treatment Guidelines[5]

	Vitamin D Screening	Vitamin D and Calcium Intake	Osteoporosis BMD Screening	BMD Threshold for Pharmacologic Intervention	Monitoring
USPSTF	Evidence is insufficient to assess the benefit/harm in Asymptomatic adults	Evidence is insufficient to assess the benefit/harm in premenopausal women and in men	Recommends screening in women age 65 and older and in younger women with significant fracture risk	Not specifically addressed; drug therapy may be considered in the primary (no previous osteoporotic fracture) or in the secondary (prior osteoporotic fracture) setting	Evidence is lacking on intervals of repeat screening
		Evidence is insufficient to assess the benefit/harm of daily supplements with >400 IU of vitamin D and >1,000 mg of calcium in noninstitutionalized postmenopausal women	Evidence is insufficient to assess the benefit/harm in men; men most likely to benefit from screening have a 10-yr risk for osteoporotic fracture greater than a 65-year-old white woman without risk factors		
NOF Advises universal counseling on risks, nutrition, exercise, and behaviors	Not specifically addressed	Women under the age of 50 • 1,000 mg of calcium from all sources daily	• Postmenopausal women and men over the age of 50 with an adult age fracture • Postmenopausal woman and men above age 50-69 based on risk factor profile • Women age 65 and older • Men age 70 and older	• Clinical or asymptomatic hip or vertebral fracture • T score ≤ -2.5 in femoral neck, total hip or lumbar spine by DXA • Postmenopausal women and men age 50 and older with low bone mass (-1.0 to -2.5) and a high-risk FRAX score (*)	BMD 1-2 years after initiating therapy & every 2 years thereafter
		Women age 50 and older • 1,200 mg calcium daily Men age 70 and younger • 1,000 mg calcium daily Men age 71 and older • 1,200 mg calcium daily Adults under the age of 50 • 400-800 IU vitamin D Adults age 50 and older • 800-1,000 IU vitamin D			

Abbreviations: USPSTF, U.S. Preventive Services Task Force; NOF, National Osteoporosis Foundation; BMD, bone mineral density.
*FRAX: Fracture Risk Algorithm; High-risk scores: 10-year hip fracture probability ≥ 3% or 10-year major osteoporosis-related fracture probability ≥ 20% based on the USA adapted World Health Organization fracture risk model.

static breast cancer and prostate cancer, respectively. Great advances have been made in understanding the molecular mechanisms of the sex hormones and hormonal influences on cancer and bone. Refinements in targeted endocrine therapy and cancer care have moved endocrine therapy into the (neo-)adjuvant setting. The goals of (neo-)adjuvant endocrine therapy are to improve disease-free and overall survival. With the use of endocrine systemic therapy to eradicate occult residual tumor cells, the skeleton is also exposed to endocrine intervention. The resulting deprivation of estrogen and androgen accelerate bone loss and increases the risk for fracture. Managing these risks are important aspects of cancer survivorship care. The effects of antiestrogen and antiandrogen cancer therapies on bone have been a subject of study for more than 20 years.[15,16] Much has been published on the effects of cancer therapy on BMD and the increased risk of fracture. Components of that literature will be reviewed here, but this is not an exhaustive review.

Breast Cancer Endocrine Therapies

Approximately 75% of breast cancers express the estrogen receptor or progesterone receptor and are considered hormone receptor positive (HR+).[17] Use of antiestrogen adjuvant therapies reduces the risk of breast cancer recurrence by approximately 30% to 50%.[18] Current guidelines recommending the use of targeted antiestrogen therapy for early-stage HR+ breast cancer include those published by the American Society of Clinical Oncology (ASCO).[19] The ASCO guideline supports the use of adjuvant tamoxifen in premenopausal and perimenopausal women with HR+ breast cancer. For women with HR+ early breast cancer who are postmenopausal, the use of an aromatase inhibitor (AI) is favored either as the sole adjuvant endocrine therapy or in sequence with tamoxifen. The menopausal status of the patient, the drug used, and the duration of treatment all affect how adjuvant breast cancer endocrine therapy will affect bone and may influence treatment decisions.

Tamoxifen is a selective estrogen receptor modulator (SERM) with both agonist and antagonist effects. In postmenopausal women, tamoxifen acts as a partial estrogen agonist on bone, stabilizing or even increasing bone mass. In a randomized placebo-controlled study 20 mg tamoxifen administered daily increased the lumbar spine BMD by 0.61% per year, whereas treatment with the placebo was associated with a 1% decrease in BMD per year (p < 0.001).[14] With longer follow-up of these patients the sample size dwindled; at 5 years there was a trend for the tamoxifen-treated group to have a higher BMD, but the difference was not significant

(tamoxifen, 0.8% increase in BMD; placebo, 0.7% decrease in BMD; p = 0.06).[20] The bone data for 10-year treatment with tamoxifen are limited. The ATLAS trial enrolled both premenopausal and postmenopausal women and randomly assigned them to either stopping tamoxifen at 5 years or continuing tamoxifen for 10 years. There were 62 fractures in the 10-year tamoxifen group and 70 fractures in the 5-year tamoxifen group. This difference did not reach statistical significance (event rate ratio 0.86; 95% CI, 0.61 to 1.21, p = 0.39) and was not analyzed based on menopausal status.[21]

In premenopausal women, tamoxifen is associated with loss of BMD. A prospective study serially monitored BMD in premenopausal women with breast cancer who were treated with chemotherapy. Women with HR+ tumors received tamoxifen and women with HR− cancers were observed as controls. At 3 years, women in the tamoxifen-treated group who retained menstrual function lost 4.6% of lumbar spine BMD whereas the controls who similarly retained menstrual function after chemotherapy had a modest gain of 0.6% in lumbar spine BMD.[22] A similar trend in BMD was seen in a randomized controlled study of healthy women treated with a chemoprevention regimen of 20 mg tamoxifen daily or placebo. In this trial the premenopausal women lost 1.44% in lumbar spine BMD per year over 3 years whereas those on placebo gained 0.24% of BMD (p < 0.001).[23]

The aromatase inhibitors (AIs) anastrozole, exemestane, and letrozole prevent the conversion of androgens to estrogens by reversibly or irreversibly inhibiting the aromatase enzyme. They are indicated for use in HR+ breast cancer in postmenopausal women and may be considered an option in women undergoing chemical ovarian ablation.[18,19] The AI-induced decrease in serum estrogen is associated with a decrease in risk of breast cancer recurrence and occurrence of new breast cancer, but is also associated with accelerated loss of BMD and an increased risk for fracture. These bone toxicities have been seen irrespective of the particular AI studied.[19,24-26] The effect of AIs on BMD contrasts with that of tamoxifen, which may have a stabilizing or positive effect on postmenopausal BMD. In a systematic review and meta-analysis, 5 years of AI therapy was associated with a 47% increase in the odds of bone fracture compared to tamoxifen (odds ratio [OR] 1.47; 95% CI, 1.34 to 1.61, p < 0.001). The absolute fracture risk was 7.5% in the AI group and 5.2% in the tamoxifen group.[27]

There has been interest in whether exemestane may not have the same magnitude of bone toxicity as the nonsteroidal AIs. The bone substudy within the phase III MA.27 study investigated whether exemestane has a superior bone sparing affect compared with anastrozole. At 2 years of follow-up, the changes in BMD did not differ between treatment arms, regardless of baseline BMD. In addition, the rates of fractures were similarly low in both arms.[28] BMD was assessed in a substudy of MAP.3, a randomized placebo-controlled study of exemestane versus placebo for the prevention of breast cancer in which 351 postmenopausal women (176 on exemestane, 175 on placebo) underwent serial BMD measure-ments. At 2 years of treatment, exemestane was associated with statistically greater bone loss in lumbar spine, hip, radius, and tibia.[29]

Ovarian ablation by chemical, radiation, or surgical means results in lower circulating levels of serum estrogens in premenopausal women with breast cancer and may be considered an adjuvant endocrine therapy.[18,30] Surgery and radiation create a permanent menopausal state whereas use of GnRH agonists (goserelin or leuprolide) provides a temporary chemically-induced menopausal state. The use of ovarian suppression in the adjuvant setting has recently been informed by the reports of two large phase III studies[31,32] and the role for ovarian ablation in adjuvant breast cancer care is still being defined.

Acute cessation of ovarian function with its sudden drop in circulating estrogen levels correlates with rapid acceleration of bone resorption and ultimately a decrease in BMD. The rate of loss is greatest initially and decreases over time. In a small study of serial BMD measurements after oophorectomy, the women had lost 18% to 19% of spine BMD at 2 years.[33] In premenopausal women participating in a randomized clinical trial comparing goserelin, goserelin/tamoxifen, tamoxifen alone or no endocrine therapy, women treated with goserelin alone experienced a 5% decrease in total body BMD at 2 years. Those treated with goserelin/tamoxifen experienced 1.4% loss, tamoxifen alone resulted in a 1.5% loss, and the control group showed a 0.3% loss.[34] These findings from small older studies are consistent with BMD changes noted in the phase III study ABCSG-12, in which premenopausal women with breast cancer were randomly assigned to goserelin/tamoxifen versus goserelin/anastrozole. There was a second randomization to zoledronic acid or not, and, as expected, treatment with 4 mg zoledronic acid every 6 months preserved BMD. At 3 years the women who were not treated with zoledronic acid but received goserelin/tamoxifen lost 9.0% of lumbar spine BMD whereas those who were treated with goserelin/anastrozole without zoledronic acid lost 13.6% of lumbar spine BMD.[35]

Chemotherapy-induced ovarian dysfunction may be temporary or permanent and is influenced by the chemotherapeutic regimen and the age of the patient. Because of the inherent difficulties in assessing residual ovarian function, chemotherapy-induced ovarian dysfunction should not be mistaken for menopause. A reference for the definition of menopause in the setting of breast cancer therapy can be found within the National Comprehensive Cancer Network breast cancer guidelines. Chemotherapy-induced ovarian dysfunction is associated with loss of BMD. The rate and duration of bone loss has not been thoroughly categorized because of differences in the definition of ovarian dysfunction, duration of study, and frequent inclusions of interventions such as bisphosphonates. The most comprehensive analysis of chemotherapy-induced ovarian dysfunction BMD studies was performed in the Cancer and Leukemia Group B (CALGB) trial 79809, which enrolled 439 premenopausal women over the age of 40 who were receiving adjuvant breast

cancer chemotherapy. Women were randomly assigned to treatment with zoledronic acid, to be given up front or in the second year of the study. Women were serially monitored for ovarian function and BMD. A total of 150 women met the study definition for chemotherapy-induced ovarian failure and completed lumbar spine BMD assessments at baseline and 1 year; 80 women in the delay zoledronic acid arm and 70 women in the up-front zoledronic acid arm. Women who were treated with zoledronic acid gained 1.2% in lumbar spine BMD whereas the untreated group lost 6.7% of lumbar spine BMD at 1 year (p < 0.001).[36]

Prostate Cancer Endocrine Therapies

The androgen receptor is expressed on prostate cancer[37] and the majority of prostate cancers are androgen-dependent and respond to endocrine therapy.[38] Androgen deprivation therapy (ADT) may be permanently induced with bilateral orchiectomy or temporarily induced by chemical ablation with GnRH agonists (leuprolide, goserlin, triporeline, or histrelin) or GnRH antagonists (degarelix).

ADT may be used in earlier stage prostate cancers that are deemed to be at high risk of recurrence. ADT may be used as neoadjuvant therapy, concurrently with radiation therapy, or as adjuvant therapy following radiation. In addition, ADT may be used in the setting of biochemical recurrence. This discussion will not cover metastatic disease or combined androgen blockage.

The hypogonadal state induced by ADT is associated with an accelerated rate of bone resorption. In general, in an older man the normal rate of loss of BMD is approximately 0.5 to 1.0% per year. With bilateral orchiectomy the rate of loss in BMD is estimated at approximately 8% to 10% over the first 1 to 2 years,[39] whereas the rate of BMD loss with ADT is 3% to 7% per year.[26] The rate of BMD loss is greatest when first starting ADT and decreases over time.

ADT is associated with an increased risk for fracture. An analysis of SEER-Medicare records of more than 50,000 men with a diagnosis of prostate cancer demonstrated a dose-dependent association between the use of GnRH agonists and the risk of fracture.[40] Nineteen percent of men who received ADT for 12 to 60 months experienced a fracture whereas only 12.6% without ADT had fractures in the same time period (p < 0.001). Men treated with one to four doses of GnRH had a fracture risk similar to those with no ADT, and those treated with nine or more doses had a fracture risk similar to that of men who underwent orchiectomy, which was associated with the highest rate of fractures. This study could not rule out pathologic fractures; however, the risk of fracture with ADT was not significantly altered when the analysis was restricted to early-stage disease. Similarly, another large database analysis of men with prostate cancer treated with or without GnRH demonstrated a significantly increased risk for fracture in those treated with GnRH; the relative risk for hip fracture with ADT was 1.76 (95% CI, 1.33 to 2.33).[41]

BONE HEALTH CARE IN THE SETTING OF ENDOCRINE THERAPY FOR BREAST OR PROSTATE CANCER

Low bone mass may be a pre-existing comorbid condition when breast or prostate cancer is diagnosed or may be induced secondary to cancer therapies. When prescribing cancer therapies that might increase the risk of fracture, counseling on the potential bone toxicity and means to mitigate that risk should be provided. Universal counseling on bone health includes providing advice on calcium and vitamin D intake, exercise, behavior (no tobacco, limit alcohol), the risk of falling, and certain medications such as steroids. These risk factors can be modified in many situations and should not be neglected as they are opportunities to optimize bone health. The management of bone health can be shared with the patient's primary care provider, as well as other medical providers such as endocrinologists. Bone health guidelines for the general public and for those affected by cancer have been published and serve as references. Examples of such guidelines include documents produced by the USPSTF,[42] National Osteoporosis Foundation,[11] American College of Physicians,[43] and European Society of Medical Oncology.[44]

Screening for risk of fracture includes obtaining a bone health history, assessing loss in height as an indicator of prior vertebral compression fractures, obtaining a personal and family history of fragility fractures, assessing calcium and vitamin D intake, and reviewing prior BMD assessments. Using information obtained by history and physical examination, the clinical team may consult the free online World Health Organization Fracture Risk Assessment Tool (FRAX), which can be used with or without BMD data.[45] This tool has similarities to Adjuvant! OnLine in that it calculates estimated risk of specific outcomes, but it does not replace additional evaluations and clinical judgment. The outcomes estimated by FRAX are the 10-year risk of either a major osteoporotic fracture or a hip fracture. Suggested thresholds for pharmacologic intervention include a 20% or greater risk of major osteoporotic fracture risk in 10 years or a 3% or greater risk of hip fracture in 10 years; however, treatment decisions must be made based on the individual's situation. FRAX is not applicable to patients on antiresorptive therapy.

The result of BMD testing may provide the diagnosis of osteoporosis or osteopenia. A low BMD is associated with a high risk of fracture and DXA is the gold standard for measuring BMD. If low bone mass is identified, consideration should be given to secondary causes of osteoporosis such as primary hyperparathyroidism or vitamin D deficiency, which may be common in women with breast cancer.[46] It is estimated that for each standard deviation drop in BMD the risk of fracture increases by 1.5- to 2.5-fold, thus making the measurement of BMD for fracture risk assessment similar to that of blood pressure for stroke.[13] DXA results can be serially monitored in treated or untreated patients. The interval between DXA scans is typically 1 to 2 years[13,26] although a longer duration may be appropriate, particularly for those on

TABLE 3. FDA-Approved Pharmacologic Therapies for the Prevention and/or Treatment of Osteoporosis*

Drug Class	Drug Name	Indications for Women	Indications for Men	Concerns/Warnings
Bisphosphonates	Alendronate	Treat or prevent postmenopausal osteoporosis	Increase bone mass in osteoporosis	Uncommon risks include hypocalcemia, osteonecrosis of the jaw, and atypical fractures. Intravenous formulations may cause acute phase reactions and renal dysfunction
	Ibandronate	Treat or prevent postmenopausal osteoporosis		
	Risedronate	Treat or prevent postmenopausal osteoporosis	Increase bone mass in osteoporosis	
	Zoledronic acid (5 mg)	Treat or prevent postmenopausal osteoporosis	Increase bone mass in osteoporosis	
Monoclonal Antibody	Denosumab (60 mg)	Treatment of postmenopausal osteoporosis with high risk for fracture. Treatment to increase bone mass in women at high risk for fracture who are receiving adjuvant AI for breast cancer	Treatment to increase bone mass in osteoporosis at high risk for fracture. Treatment to increase bone mass in men at high risk for fracture receiving ADT for non-metastatic prostate cancer	Uncommon risks include hypocalcemia, osteonecrosis of the jaw, and atypical fractures
Hormonal	Raloxifene	Treat or prevent postmenopausal osteoporosis		In the ATAC trial,[54] the combination of SERM (tamoxifen) and AI did not have the same efficacy as the AI alone
	Menopausal hormonal therapy, estrogen and estrogen-progestin combination Duavee (estrogen combined with bazedoxifene)	Prevent postmenopausal osteoporosis		Exogenous estrogen use is generally to be avoided because of concern for an increased risk of breast cancer recurrence
	Teriparatide (parathyroid hormone)	Postmenopausal osteoporosis with high risk for fracture	Primary or hypogonadal osteoporosis at high risk for fracture	Not to be used by those who have received external beam or implant radiation because of increased risk for osteosarcoma. Not to be used by those with bone metastases

Abbreviations: ATAC, Arimidex, Tamoxifen, alone or in combination.
*Indications for glucocorticoid-induced osteoporosis are not presented here.

antiresorptive therapy or those with low risk of fracture. Interesting data generated from the Study of Osteoporotic Fractures demonstrated that postmenopausal women with normal BMD at baseline transition to osteoporosis at a slower rate than postmenopausal women with severe osteopenia (T score -2.0 to -2.49).[47] These data suggest that the interval of monitoring BMD might be influenced by the baseline DXA result. However, the data do not lend themselves directly to patients with breast cancer or prostate cancer receiving endocrine therapy.

Osteoporosis may be underdiagnosed.[6] A SEER-Medicare study of health care utilization of DXA in women over the age of 65 with a history of nonmetastatic breast cancer revealed that less than 10% of the study population underwent BMD testing.[48] Another SEER-Medicare study suggests that the frequency of BMD screening was less than 20% in the year 2002.[49] Screening of men for osteoporosis is also occurring at a low rate. A SEER-Medicare study of men on ADT for non-metastatic prostate cancer revealed fewer than 10% of patients with BMD measurements.[50]

BMD thresholds for pharmacologic intervention typically include osteoporosis (T score ≤ -2.5) or low bone mass and additional risk factors for fracture. Once the risk for a fragility fracture is sufficiently high to warrant pharmacologic in-

tervention in a patient with early-stage breast or prostate cancer, there are data supporting the use of bisphosphonates or denosumab at FDA-approved dosing and intervals. Discussion of the use of bisphosphonate therapy as an anticancer therapy is outside the scope of this discussion. Clinical trials ranging from phase II to phase IV have demonstrated the ability of bisphosphonates or denosumab to preserve or improve BMD in the setting of endocrine therapy for breast or prostate cancer. Options for pharmacologic intervention, including therapies to avoid, are outlined in Table 3. Published cancer and bone health guidelines produced by cancer organizations include the ESMO bone health guideline[44] and the NCCN Task Force Report, Bone Health in Cancer Care.[51] The duration of antiresorptive therapy will be influenced by the response obtained, the duration of endocrine therapy, and the fracture risk. It is of note that the FDA recommends periodic re-evaluation of the need for continued bisphosphonate therapy, particularly in patients who have been treated for over 5 years. This reflects concern for long-term toxicities such as subtrochanteric and diaphyseal femur fractures. Patients receiving bisphosphonates or denosumab in the setting of endocrine therapy for early-stage breast or prostate cancer are at risk of experiencing toxicities from antiresorptive therapy per packet insert warnings and precautions.

FUTURE DIRECTIONS

With our aging population, it is expected that the number of people affected by osteoporosis and with cancer will increase. The need to co-manage these diagnoses will continue into the foreseeable future. Areas of osteoporosis research include targeting sclerostin and thereby potentially inducing osteo-anabolic activity, which may or may not be appropriate for use in patients with a history of breast or prostate cancer. As novel bone signaling pathways are targeted, the effect on cancer signaling must also be considered. Likewise, as novel anticancer therapies are developed, their effects on bone health should be investigated.

There are insufficient data to guide all possible clinically relevant bone and endocrine situations faced in the medical oncology clinic. Indeed, there are many questions that have not been formally studied, most notably where fractures are the primary endpoint. A fundamental goal of bone health care is to prevent fractures. BMD is a surrogate measurement used in risk assessment for fracture but is not the endgame. It can be challenging to study rates of fractures because of the large number of patients and the long duration of follow-up needed. Thankfully, it is very likely that in the future of "Big Data" and the ASCO program CancerLinQ, knowledge of the bone health of every patient will provide answers to fracture-related and other questions. There is reason to be optimistic that CancerLinQ and future research will reveal patterns of events and patterns of care that will inform future guidelines to improve bone outcomes.

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Endocrine Therapy and Its Effect on Sexual Function

Shari Goldfarb, MD

Breast cancer is the most common malignancy in women and it is estimated that more than 230,000 invasive cancers will be diagnosed this year.[1] Approximately three-quarters of all invasive breast cancers are estrogen and/or progesterone receptor–positive. Endocrine therapy is the mainstay of treatment for both prevention and treatment of hormone receptor–positive breast cancers. Hormone therapy is the oldest targeted therapy and was initially described by both Sir George Beatson[2] and Albert Schinzinger more than 100 years ago when they noted that bilateral oophorectomies resulted in tumor regression in premenopausal women with advanced breast cancer.[3] A key therapeutic approach for treatment of both metastatic and adjuvant hormone receptor–positive breast cancer is estrogen deprivation. This can be achieved by suppressing ovaries, decreasing estrogen production, blocking estrogen at the level of the receptor, or by degrading estrogen receptors. Endocrine therapy is also used for the treatment of some hormone receptor–positive endometrial cancers. Commonly used endocrine therapies can have extensive sexual side effects that affect quality of life (QoL).[4-6] This article will discuss different endocrine therapies, their effect on sexual function, and treatment options to improve sexual health.

ENDOCRINE THERAPY

Tamoxifen

Tamoxifen is a selective estrogen receptor modulator (SERM), which has both partial estrogen agonist and antagonist activity. It competitively binds to the estrogen receptor (ER), which leads to interrupted cell proliferation and ultimately cell death by causing cells to remain in the G1 phase of the cell cycle.[7] Tamoxifen mimics estrogen in certain tissues, such as the bone and uterus, which has both beneficial and adverse effects. For example, tamoxifen improves lipid profiles and prevents bone demineralization, increasing bone density. However, it also increases the risk of uterine cancer by 2.5 times and the risk of a thromboembolic event by 1.9 times.[8] In breast tissue, tamoxifen antagonizes the action of estrogen, which both treats breast cancer and decreases the risk of a new primary breast cancer. The U.S. Food and Drug Administration (FDA) initially approved tamoxifen for the treatment of metastatic breast cancer in 1977 and for adju-

vant therapy in 1990. Tamoxifen was subsequently approved in 1999 by the FDA for the primary prevention of breast cancer.

Aromatase Inhibitors

Aromatase is an enzyme of the cytochrome P450 (CYP) family and the product of the CYP19 gene, which is the primary enzyme used for the synthesis of estrogen in postmenopausal women. It is found in peripheral tissues including muscle, normal breast tissue, breast cancer tissue, fat, liver, and brain.[9] Aromatase inhibitors (AIs) decrease estrogen production by blocking aromatase and thus decrease peripheral conversion of testosterone to estradiol and androstenedione to estrone. Third generation AIs decrease estrogen production by over 95%, resulting in subphysiologic levels of estrogen. AIs are only effective in postmenopausal women because they are unable to overcome ovarian aromatase activity.

Classification of the Aromatase Inhibitors: Nonsteroidal and Steroidal Agents

AIs are classified into two different types (1) nonsteroidal or (2) steroidal, which differ in their mechanism of interaction with the enzyme aromatase.[10] Nonsteroidal AIs bind reversibly to the heme portion of the CYP aromatase enzyme, resulting in competitive inhibition.[11] These type II inhibitors include the imidazole, fadrozole, and the imide, aminoglutethimide, as well as the triazoles including letrozole, anastrozole, and vorozole. Steroidal AIs are similar in structure to the true enzyme substrate, androstenedione, and bind irreversibly to the substrate binding domain of the aromatase enzyme, which results in a permanent inactivation of the aromatase enzyme.[12] These type I inhibitors include exemestane, formestane, and atamestane. There is no clinical evidence that demonstrates one mechanism of inhibition is superior to the other.

There are first, second, and third generation AIs based on their specificity and potency for aromatase enzyme inhibition.[13] The third generation AIs are the most potent and specific and include anastrozole, letrozole, and exemestane. They are widely used because they have improved tolerability and efficacy compared with prior generations. The third generation AIs have long half lives (anastrozole and letrozole ap-

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proach 48 hours and exemestane 27 hours) allowing for daily dosing.

Fulvestrant

Fulvestrant is a selective estrogen receptor degrader that was FDA approved in April 2002 for the treatment of hormone receptor–positive metastatic breast cancer. Fulvestrant downregulates the ER by binding to it and inducing a change in conformational shape that prevents ER dimerization, resulting in the loss of cellular ER.[14,15]

OVARIAN SUPPRESSION

In premenopausal women with hormone receptor–positive metastatic breast cancer, estrogen deprivation is a key therapeutic strategy. Since the ovaries are the predominant sites of estrogen synthesis in premenopausal women, a patient's ovaries must be medically suppressed or surgically ablated via bilateral oophorectomies as part of her breast cancer treatment.[16,17] Estrogen levels are immediately and permanently reduced to the postmenopausal range in all women after surgical castration, whereas medical ablation is slower and may take several weeks before estrogen is fully suppressed. Medical ablation is performed by using a luteinizing hormone-releasing hormone (LHRH) analog, which acts on the hypothalamic-pituitary-ovarian axis and suppresses circulating estrogen levels.[18] LHRH analogs include goserelin, buserelin, triptorelin, and leuprolide and are administered as either monthly or every 3 month injections.[18] Medical suppression is reversible once the LHRH agonist is discontinued. After the initial administration of an LHRH analog, there is a surge in both estrogen and gonadotropin levels, which may cause a tumor flare phenomenon.

More recently with the presentation and publication of data from the Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane trial (TEXT) studies, ovarian suppression is being considered as adjuvant therapy for some young premenopausal women with high-risk early-stage disease.[19] The TEXT trial randomly assigned premenopausal women with early-stage hormone receptor–positive breast cancer to receive either 5 years of adjuvant therapy with triptorelin in combination with tamoxifen or triptorelin in combination with exemestane. The SOFT trial randomly assigned premenopausal women with early-stage hormone receptor–positive breast cancer to receive either ovarian suppression with exemestane, ovarian suppression with tamoxifen, or tamoxifen alone for 5 years. In the SOFT trial, ovarian suppression could be achieved with either triptorelin, ovarian irradiation, or bilateral oophorectomy.

The original plan was for separate statistical analyses for the TEXT and SOFT studies followed by a planned combined analysis of the ovarian suppression plus tamoxifen versus ovarian suppression plus exemestane cohorts.[19] However, as a result of low recurrence rates, in 2011 the studies were amended to make the primary analysis a combined analysis. The combined analysis had a median follow-up of 68 months. In the ovarian suppression plus exemestane cohort, disease-free survival at 5 years was 91.1% compared with 87.3% in the ovarian suppression plus tamoxifen arm (hazard ratio [HR] for disease recurrence, second invasive cancer, or death, 0.72; 95% CI, 0.60 to 0.85; $p < 0.001$). There was no significant difference in overall survival between the two treatment groups (HR for death in the exemestane plus ovarian suppression group, 1.14; 95% CI, 0.86 to 1.51; $p = 0.37$).

SEXUAL SIDE EFFECTS OF ENDOCRINE THERAPY

In premenopausal women, the primary site of both estrogen and testosterone synthesis is the ovaries. However, hormones play essential roles in central and peripheral aspects of female sexual function, sexuality, and integrity of the urogenital tract. When premenopausal women undergo either medical or surgical ovarian ablation for the treatment of breast cancer, they are abruptly put into menopause. This can also occur with chemotherapy-induced amenorrhea and menopause, which may be transient or permanent. Premature menopause often causes greater intensity and duration of symptoms than women undergoing natural menopause. Hot flashes, vaginal dryness, urogenital atrophy, dyspareunia, decreased libido, and changes in sexual response have been shown to negatively affect QoL, compliance with medication, and overall outcome. Iatrogenic menopause often causes lower steroid levels than natural menopause. For example, testosterone levels in natural menopause are around 290 pg/mL, but are 110 pg/mL in iatrogenic menopause, which substantially worsens sexual function. Likewise, estradiol, androstenedione, and dehydroepiandrosterone (DHEA) are present at lower levels as a result of iatrogenic menopause compared with natural menopause.

Treatment with endocrine therapy can have substantial sexual side effects, even in women who are already in menopause.[13] In postmenopausal women treated with AIs, marked alteration of the vulvar anatomy has been seen clinically in combination with vaginal dryness and dyspareunia that can lead to a change in the physical capacity for sex.[20] It is unclear why some women are more sensitive to endocrine therapy than others, but it may be secondary to polymorphisms in the ER and androgen receptors that cause a differential ability to utilize the small amount of available estrogen that is present.[21]

Tamoxifen, AIs, and fulvestrant all have sexual side effects. Tamoxifen can cause a clear vaginal discharge, vaginal and/or endometrial bleeding, vaginal dryness, vaginitis, dyspareunia, lowered orgasmic intensity, hot flashes, and decreased libido.[22,23] AIs suppress estrogen to subphysiologic levels, which causes worse vaginal dryness, dyspareunia, urogenital atrophy, decreased libido, lowered orgasmic intensity, and changes in sexual response compared with tamoxifen. In women with breast cancer on AIs for extended periods of time, gynecologists have also seen more extreme sexual side effects of therapy such as severe narrowing or stenosis of the vaginal introitus, clitoral atrophy, adhesions, phimosis, and decrease in vaginal length that may be a result of a loss of collagen, glycogen, and other proteins in the hypoestrogenic urogenital epithelium.[24,25] Since baseline gynecologic examinations are rarely performed before the initiation of AIs, the extent of architectural changes and stenosis attributable to the medication is difficult to quantify. It is unknown if these changes are reversible after discontinuing AI therapy or if they persist or worsen over time. Fulvestrant tends to have fewer sexual side effects than tamoxifen and AIs; however, fulvestrant can cause vaginal dryness, hot flashes, dyspareunia, and/or decreased libido.

Breast cancer and its treatment can also cause body image concerns including alopecia, surgical scars, change in weight, loss of femininity, decreased nipple sensation, and chest wall numbness, which all affect a woman's sexuality. Libido and sexual function is further impaired by hormonal changes, amenorrhea, anxiety, a change in relationship with a partner, depression, family distress, neuropathy, impaired immune response, and fatigue.[26,27]

ASSESSMENT OF SEXUAL FUNCTION IN WOMEN WITH BREAST CANCER

Clinicians should discuss sexual health with all women with breast cancer and survivors of the disease, including those who are single and older. Counseling for prevention and treatment of sexual problems will vary based on the time at which the patient presents for care. It would be helpful to have a baseline assessment of sexual function before or at the time of a cancer diagnosis to have a better understanding of the effect of a breast cancer diagnosis and each subsequent treatment (surgery, chemotherapy, radiation therapy, and endocrine therapy) on sexual function. However, gynecologists, medical oncologists, breast surgeons, radiation oncologists, and plastic surgeons do not routinely assess and document a woman's sexual function. Ideally, it should be a part of a routine annual gynecologic exam.

It would improve patient care and research by having an accurate assessment of baseline sexual function. This can be assessed on a patient review of systems form briefly with one question or in greater depth with several questions. For example, sexual concerns can be added to a check-box review of systems form and patients can answer yes or no. This can be the starting point to stimulate a discussion, to prompt more in-depth questioning, or to refer to a sexual health provider. If there is more time or room on the form, other questions can be added to assess hot flashes, vaginal lubrication, dyspareunia, postmenopausal bleeding, decreased libido, and recurrent urinary tract infections. It has been shown that patients will not initiate sexuality discussions, but want health care providers to discuss this topic. If clinicians neglect to discuss sexual problems, they will often go unaddressed.

INTERVENTIONS TO IMPROVE SEXUAL FUNCTION

Sexual problems in women with breast cancer can be especially challenging to treat and often requires a multidisciplinary approach. Treatment and prevention of sexual dysfunction from cancer and its therapy is best addressed with a team including a gynecologist, sex therapist, psychologist, and physical therapist who all work together and in collaboration with the patient's oncologist and/or primary care physician.

Vaginal atrophy and lubrication problems in breast cancer survivors are prevalent and its management is complex.[24] Although the most effective agent for menopause-induced vaginal atrophy is estrogen,[28] women with breast cancer are discouraged from using systemic estrogens because of an increased risk of disease recurrence.[29-31] Some safe and potential nonhormonal treatments include moisturizers, lubricants, counseling, sex therapy, physical therapy for pelvic floor disorders, altering contributing medications (e.g., selective serotonin reuptake inhibitors [SSRIs]), and mechanical devices/vibrators.[32] The standard of care for the treatment of vaginal atrophy in women with hormone receptor–positive cancers is currently moisturizers. At this time, the use of intravaginal estrogen, testosterone, and DHEA is controversial and further studies must be conducted to evaluate its safety in women with breast cancer who are receiving endocrine therapy, especially AIs. Randomized control data are lacking and are required to develop evidence-based treatment for sexual dysfunction in patients with cancer and to ultimately improve patient outcomes and QoL.

Lubricants

Lubricants are recommended to reduce friction and pain during vaginal penetration for women with vaginal atrophy and/or dryness. They are used on the woman and her partner (or sexual device) as needed before penetration. There are three different classes of lubricants: water-based, oil-based, and silicone-based. Water-based lubricants decrease pain

and friction with vaginal and anal intercourse and improve the sensation of dryness, but are shorter-acting and tend to dry quickly. Silicone-based lubricants tend to work better than water-based lubricants for anal intercourse because they are longer lasting and give a lusher feel. However, they can not be used with silicone vibrators, dilators, or other silicone toys. Both water- and silicone-based lubricants are safe to use with latex condoms, but oil-based lubricants may render latex condoms ineffective. Oil-based lubricants such as olive oil and vegetable oil tend to be the lubricant of choice for oral sex, but can increase risk of vaginal infections. Parabens and glycerines in lubricants can cause contact dermatitis, skin irritation, or a burning sensation. There are hundreds of lubricants available and each woman can chose the one that works best for her. Lubricants can also be used in combination with moisturizers.

Moisturizers

For postmenopausal women taking an AI with subphysiologic levels of estrogen, chronic vaginal dryness (e.g., genitals feel dry, irritated, pruritic, and/or painful during intercourse, gynecologic exams, and even with walking or sitting) is common and lubricants are often not enough to treat it.[33] Nonhormonal moisturizers are a safe treatment for vaginal dryness and atrophy in both pre- and postmenopausal women with breast cancer.[34-36] Intravaginal moisturizers (gels, creams, suppositories, or ovules) should be used every two to three nights to hydrate the vulvo-vaginal tissues, achieve optimal absorption, and minimize leakage. They also improve vaginal pH, dryness, elasticity, irritation, discomfort, and pruritus and are not solely used for sexual contact.[33,37] Regular treatment for 8 to 12 weeks is needed to see maximum benefit. The most commonly used moisturizer in the United States and Canada is Replens.

Replens is a polycarbophil-based gel that binds to the vaginal epithelium and delivers water and electrolytes to the underlying cells.[37] It normalizes vaginal pH, improves morphology of epithelial cells in vaginal smears, and alleviates vaginal symptoms.[37,38] Patients should be educated about the differences between lubricants and moisturizers to ensure proper usage of both types of treatment. In women with hormone receptor–positive breast cancer receiving endocrine therapy, there is currently limited information regarding the efficacy of moisturizers and if benefits can be maintained over time. Several small clinical trials performed in postmenopausal women with vaginal atrophy evaluated the efficacy of Replens, but did not follow patients long enough to determine effectiveness over time.[34,37] Clinical trial results with Replens are variable. Two small studies in postmenopausal women showed an improvement in vaginal discomfort, pruritus, and dyspareunia equivalent to the relief seen with intravaginal estrogen creams.[34,39] Two other small double-blind studies (one in women with breast cancer) did not show better efficacy with Replens compared with lubricants.[40,41] Replens has also been used as part of a multifaceted intervention to alleviate menopausal symptoms in women

with breast cancer, but the independent effect of Replens was not analyzed.[42]

Hyaluronic Acid

Hyaluronic acid is the main component of other moisturizers such as Hyalogyn and Hyalofemme. It is a high molecular weight glycosaminoglycan that moisturizes the vaginal epithelium by retaining high amounts of water and creating an extracellular water film with swelling.[43,44] By delivering water and electrolytes into underlying cells, hyaluronic acid improves epithelial elasticity and hydration.[45] In a group of postmenopausal women without cancer, an intravaginal gel containing hyaluronic acid was compared with vaginal 17-β estradiol tablets. Both treatments demonstrated an improvement in vaginal pH and atrophy with relief of vaginal symptoms. Two small pilot studies suggest possible benefits of hyaluronic acid in women with endometrial or breast cancer.[45] Further research on the efficacy of hyaluronic acid in the breast cancer population is needed.

Ospemifene

Ospemifene, a SERM with tissue-selective effects, was FDA approved on February 26, 2013 for the treatment of dyspareunia in postmenopausal women. Two phase III clinical trials showed that the efficacy of ospemifene was substantially greater than placebo in terms of improving dyspareunia, vaginal pH, and increasing superficial cells.[46,47] The most frequently reported treatment-related adverse event was hot flashes, which were reported in 6.6% of study participants in the ospemifene cohort compared with 3.6% in the placebo treatment group. Ospemifene can also increase the risk of endometrial cancer and blood clots, including deep vein thrombosis, pulmonary emboli, and cerebrovascular events. The effect of ospemifene on breast tissue has never been studied clinically and until it is evaluated, it should not be given to women with a history of breast cancer.

Dilators

AIs can cause marked alteration of the vulvar and vaginal anatomy causing vaginal stenosis from loss of rugae, which transforms the vaginal canal into a smooth, inflexible tube. Stenosis causes the vagina to feel stretched, painful, or taut during vaginal penetration. Vaginal stenosis is best treated with a multimodal approach using dilators, moisturizers, lubricants, pelvic floor physical therapy, and patient education. Dilators are available in sets of increasing size and are used for a gradual stretching process starting with the smallest dilator. They alleviate anxiety and improve a woman's confidence that something can comfortably be placed into the vagina without discomfort.[33] Dilators are essential for maintaining vaginal health if a patient is not sexually active or lacks a partner, treating vaginal pain, and improving tolerability of pelvic examinations.[33] Compliance with dilators is poor, but women are more likely to be compliant if they believe dilators will make their pelvic exams more comfortable[48] or if they are using vaginal health promotion strategies, such as lubricants (p = 0.029) or vaginal moisturizers (p <

0.001).[49] In conjunction with pelvic floor physical therapy, dilator therapy appears to be most effective.

Pelvic Floor Exercises

Strengthening the pelvic floor may have restorative effects and improve arousal.[33,50] Pelvic floor exercises, such as contraction and relaxation of vaginal and pelvic muscles, improve sexual function by helping pelvic muscles relax during penetration, thereby improving dyspareunia from pain associated with reflexively tightening. Improving blood flow to the pelvic floor from exercises, self-stimulation, and/or vibrator use also benefits sexual function by using the arousal response.[33] Pelvic floor physical therapy and/or biofeedback may be useful for treating vaginal pain, strengthening pelvic floor muscles, improving circulation for arousal, and providing feedback regarding these issues.[33,50,51]

Antidepressants

Women with breast cancer are frequently treated with antidepressants for depression, anxiety, and management of their hot flashes. Many SSRIs are extremely helpful in treating psychologic difficulties, but cause sexual side effects.[52,53] Therefore, a conversation about the risk and benefits of SSRIs should occur before prescribing these medications. A study in patients with cancer showed that up to 79% of patients were receiving one or more psychotropic medications.[54] SSRI-induced sexual dysfunction may improve with phosphodiesterase type 5 inhibitor treatment, but this therapy has never been studied in patients with cancer and the medications are not FDA approved for this indication.[55] Bupropion is an antidepressant that does not have the adverse sexual side effect profile of most SSRIs and has been shown to actually improve overall sexual satisfaction, arousal, orgasm intensity, and desire.[55] An effective treatment strategy is to change a patient to bupropion from a different SSRI, if they are experiencing sexual side effects.

Psychologic Treatment

During endocrine therapy, patients with cancer often experience persistent sexual difficulties (e.g., dyspareunia, difficulty with lubrication, decreased libido) and attention to their effect on QoL should be an essential part of their clinical care. Sexual function and a person's sexual self-schema can also be adversely affected by depression and distress that often accompany a breast cancer diagnosis.[56,57] Therefore, it is essential to screen for psychologic problems and intervene early to improve a patient's confidence, psychologic well-being, and self-perception during and after treatment. Counseling and/or sex therapy can be effective treatment options to help patient's cope and adjust to changes, especially when performed in combination with other treatment strategies. Therapy can help a woman understand the effect of breast cancer and its treatment on sexuality, reduce fear about intimacy, learn strategies to address pain (i.e., intravaginal moisturizers and dilator therapy), promote vaginal health, increase sexual knowledge, expand the sexual repertoire, and promote positive sexual identity. Psychologic and physical consequences of cancer that affect sexuality and sexual function should be addressed proactively with all patients with cancer. Therapy can also help a patient cope with an altered body image, decreased self-esteem, depression, anxiety, and fatigue.

Sensate Focus is a technique used for women experiencing dyspareunia that helps to reduce anxiety associated with sexual touch. Sexual function for women is often multifactorial in nature with both a physical and mental component. This is evident when an individual overcomes sexual challenges despite physical impairments through adaptation. For example, a recent mindfulness intervention demonstrated improvement in the perception of arousal, even when no physical improvements in engorgement were noted.[58] In female patients with cancer, decrease distress was associated with increased sexual satisfaction.[59] Psychologic interventions appear to be effective, but additional randomized controlled trials are necessary to develop a standardized evidence-based approach to treatment.[60]

Hormone Replacement Therapy

The use of intravaginal estrogens, testosterone, and DHEA in women with hormone receptor–positive breast cancer is controversial. Several small studies have been performed and are ongoing, but it is unlikely that a large randomized study evaluating safety will ever be performed.[61-64] At this time, intravaginal hormone therapy should only be considered as a last resort after the failure of all nonhormonal options. A discussion of the risks, benefits, side effects, and alternatives to hormone therapy is required before initiating treatment so patients can make informed decisions. It is a balance between the perceived need for treatment and concerns about the therapy.

Investigational Treatments

Currently there are no FDA-approved medications for decreased libido, arousal, or orgasmic difficulties in women. However, this is an area of active drug development by pharmaceutical companies and both investigational nonhormonal and hormonal treatments are being studied. Bremelanotide or PT 141 is a promising nonhormonal agent for female sexual interest/arousal disorder. It is a melanocortin 1 and 4 receptor agonist that binds to the melanocortin 4 receptor in the hypothalamus. Flibanserin, a 5-HT1A receptor agonist and 5-HT2A receptor antagonist, is another nonhormonal drug being studied for treatment of hypoactive sexual desire disorder. The combined formulation of sildenafil plus testosterone, as well as buspirone plus testosterone, are two hormonal agents that are being studied for hypoactive sexual desire disorder, low sexual motivation, and insensitivity to sexual cues.

CONCLUSION

As women live longer after a breast cancer diagnosis and treatment, attention to QoL and symptoms are of increasing

importance both during treatment and throughout survivorship. Well-conducted research is needed to improve prevention, diagnosis, and treatment of female sexual dysfunction throughout breast cancer treatment and survivorship. In addition, more evidence about the short and long-term sexual side effects of endocrine therapy is needed to appropriately counsel patients about the relative morbidity of cancer treatment strategies. Clinical trials are needed to identify safe and effective interventions to ameliorate sexual dysfunction and ultimately improve patient outcomes through evidence based treatment. There are currently no FDA approved medications for decreased libido, arousal, or orgasmic difficulties in women. Pharmacologic medications for treating female sexual dysfunction lag behind male therapies, but there are many drugs in development that will hopefully benefit women in the future.

Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

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PATIENT AND SURVIVOR CARE

Moving Survivorship Care Forward: Lessons from Quality Measures

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Assuring Quality Cancer Survivorship Care: We've Only Just Begun

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OVERVIEW

Clinical practice guidelines, quality metrics, and performance improvement projects are the key tools of the national movement to improve and assure quality cancer care. Each of these evaluation instruments is intended to assess quality from a unique perspective, including that of the individual provider, the practice/hospital, and the health care system. A number of organizations have developed or endorsed quality measures specific to cancer, however, these have not formally included survivorship measures. Fortunately, the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network, the American Cancer Society, and the American College of Surgeons (ACoS) have taken a leadership role in developing survivorship guidelines and quality metrics. Both ASCO and ACoS have focused their efforts on the treatment summary and care plan, a document that was proposed in the 2006 Institute of Medicine report on cancer survivorship. ASCO has proposed a care plan template for implementation and incorporation into the electronic health records (EHR), which will lend itself to structure, process, and outcome measurement. ACoS, conversely, has included the care plan in its cancer program standards with annual evaluation metrics. In addition, ASCO has developed a number of key survivorship-relevant metrics as part of its Quality Oncology Practice Initiative (QOPI), a tool developed to measure quality cancer care and assess adherence to guidelines across academic and community practices. Together, these efforts will direct us to more effective ways to disseminate guideline recommendations and to better methods of assessing quality survivorship care nationally.

Increasingly, the field of oncology is focused on the implementation of strategies to improve care with an emphasis on evaluation. However, this process of implementation and evaluation is not linear; rather, it is a cyclical process in which, ideally, evidence is translated into practice and practice is reviewed and improved on the basis of evaluation, which in turn leads to new research hypotheses. Clinical practice guidelines (CPGs), quality metrics, and performance improvement projects are the key tools of this national movement to improve and assure quality cancer care. As identified in the 2013 Institute of Medicine report, *Delivering High-Quality Cancer Care*, cancer quality measures are intended to "provide objective descriptors of the consequences of care and transform the nebulous concept of 'good medicine' into a measurable discipline."[1] Identifying and assessing quality require measures that assist and support health care systems, practices, and clinicians. Each of these instruments of evaluation is intended to evaluate quality from a unique perspective. For example, CPGs translate research results into evidence-based guidance for clinicians; performance improvement projects are operational at the local level as a means of making improvements, often at the site of care.[1] Quality metrics are intended to evaluate the quality of clinician and/or practice performance compared with recommended practice, with a focus on identifying areas for improvement.

In support of this quality movement, a number of professional and nonprofit organizations have developed or endorsed quality measures that are specific to or applicable to cancer for use in performance improvement and national reporting programs. Notably, the National Quality Forum (NQF), through funding from public and private sources beginning in 2009, has endorsed more than 62 cancer-specific measures that were developed by professional medical organizations through a consensus process.[2,3] The Agency for Healthcare Quality and Research (AHRQ) through its National Quality Measures Clearinghouse has set up a repository that includes hundreds of cancer-specific measures that have been developed by NQF and other national and international organizations.[4] The scope of these cancer-specific measures, however, are focused on screening, diagnosis and staging, initial treatment, and end-of-life issues, such as symptom management. Neither organization currently includes measures that specifically focus on the cancer survivorship period.

TABLE 1. Quality Metrics: Cancer Care

Type	Description	Benefits	Challenges
Structure	Measures settings in which clinicians practice: resources, organizational structure (such as models of care)	Identifies core infrastructure needed for high-quality care	Difficult to compare across settings; implications for patient outcomes not always clear
Process	Measures delivery in defined circumstances (screening, psychosocial evaluation, care planning)	Encourages evidence-based care; straight forward to measure	Need to consider patient choices and contraindications; implication for patient outcomes not always clear
Clinical Outcome	Measures personal health and functional status as a consequence of interaction with health care system	Allows assessment of multiple end points of care	Need to risk adjust for comorbidities; difficult to compare across settings with variable populations
Cost	Measures resources required to deliver care and the effect on patient, family, and payers	Allows parties to weigh relative values of treatment options when combined with outcome measures	Difficult to measure true cost of care; costs vary by perspective (patient, payer, society)
Patient-Reported Outcomes	Measures patient perceived physical, mental, and social well being on the basis of information that comes directly from the patient	Integrates patient voice into medical decisions	Some outcomes are outside the scope of clinical care

Adapted with permission from "Delivering High-Quality Cancer Care," by the National Academy of Sciences, 2013,[1] courtesy of the National Academies Press, Washington, DC.

Yet, with this increased emphasis on measuring quality and improving cancer care, we also have growing attention to the needs of cancer survivors. This timely convergence of two important issues raises a number of important questions about how the focus on quality, already in place during cancer therapy, applies to survivorship care and services. We know that the number of cancer survivors is soon to be 19 million in 2024, and we have an active advocacy community for patients with cancer to voice their need for healthcare providers to pay attention to their post-treatment psychosocial and medical needs.[5] However, is it necessary to be concerned about measuring the quality of care in the post-treatment period? Is there a set of services that are known to be effective and/or important to the cancer survivor? In the absence of established evidence, can consensus guidance be developed to guide care and its evaluation? If so, how do we begin to focus on a parsimonious set of metrics that can be measured and will make a difference in the health of the cancer survivor? Where do we stand with respect to quality metrics for cancer survivors? Do we begin with process measures, or are we ready for the outcome measures described in Table 1? This is the challenge before us and the focus of this brief paper.

Survivorship is relatively young as a formal period along the cancer care continuum and, as such, has only recently been considered by national organizations that develop oncology guidelines and quality metrics. At the forefront in cancer survivorship guideline development are the American Cancer Society, the National Comprehensive Cancer Network (NCCN), and ASCO. Each of these leaders in oncology has taken a unique approach to developing guidelines, focusing on either a disease-specific approach or a symptom approach to survivorship care. In addition to a growing body of guidelines, two professional societies, ASCO, through its QOPI, and ACoS, with its Commission on Cancer (CoC) Cancer Program Standards, have developed cancer measures that include metrics specific to the survivorship period.[6,7] The next section of the paper will highlight the focused efforts of these two organizations.

KEY POINTS

- Increasingly, oncology is focused on the implementation of strategies to improve care, with an emphasis on evaluation.
- Survivorship-specific measures are essential to include in the suite of cancer guidelines and metrics to assure quality care during this period.
- Survivorship care plans need to be integrated into standard cancer care, and electronic health records can facilitate this implementation.
- The ASCO Quality Oncology Practice Initiative is an excellent mechanism to evaluate how well physician practices adhere to quality measures, including survivorship measures, over time.
- More effective ways to disseminate guideline recommendations and additional tools to measure quality are needed, especially in the area of cancer survivorship.

INTEGRATION OF SURVIVORSHIP CARE PLANS INTO ELECTRONIC HEALTH RECORDS

Survivorship care plans (SCPs), including the treatment summary and plan of follow-up care, were identified as tools to foster communication and coordination of care among the patient, oncology team, and primary care provider in the 2006 Institute of Medicine report, *From Cancer Patient to Cancer Survivor: Lost in Transition*.[8] However, adoption has been slow and inconsistent.[9] A number of barriers to adoption include the complexity of the SCP templates, unreimbursed time to complete the SCP, and a lack of a systematic approach to dissemination and implementation.[10] Many of these barriers can be addressed with the use of EHRs yet raise

TABLE 2. Minimum Data Elements to Be Included in a Survivorship Care Plan

Treatment Summary
Contact information of the treating institutions and providers
Specific diagnosis, including histologic subtype, when relevant
Stage of disease at diagnosis
Surgery (yes/no); if yes:
Surgical procedure with location on the body
Date(s) of surgery (year required, month optional, day not required)
Chemotherapy (yes/no); if yes:
Names of systemic therapy agents administered (listing individual names rather than regimens)
End date(s) of chemotherapy treatment (year required, month optional, day not required)
Radiation (yes/no); if yes:
Anatomic area treated by radiation
End date(s) of radiation treatment (year required, month optional, day not required)
Ongoing toxicity or side effects of all treatments received at the completion of treatment (Any information concerning the likely course of recovery from these toxicities should also be covered)
For selected cancers, genetic/hereditary risk factor(s) or predisposing conditions and genetic testing results, if performed
Follow-up Care Plan
Oncology team member contacts, with location of the treatment facility (repeat only if separate document)
Need for ongoing adjuvant therapy for cancer
Adjuvant therapy name
Planned duration
Expected side effects
Schedule of follow-up–related clinical visits (to include who will provide the follow-up visit and how often and where this will take place)
Cancer surveillance tests for recurrence (to include who is responsible for ordering/carrying out the test, the frequency of testing, and where this will take place)
Cancer screening for early detection of new cancers, to be included only if different from the general population (to include who is responsible for carrying out screening, the frequency of testing, and where this will take place)
Other periodic testing and examinations (Rather than outlining specific testing, the group suggested an inclusion of a general statement to "continue all standard non–cancer-related health care with your primary care provider, with the following exceptions: [if there are any]")
Possible symptoms of cancer recurrence (Rather than including a list of possible symptoms, the group suggested inclusion of a general statement, "Any new, unusual, and/or persistent symptoms should be brought to the attention of your provider")
A list of likely or rare but clinically significant late effects and/or long-term effects, if known, that a survivor may experience based on his or her individual diagnosis and treatment (including symptoms that may indicate the presence of such conditions)
A list of items (eg, emotional or mental health, parenting, work/employment, financial issues, and insurance) should be covered with standard language stating that survivors have experienced issues in these areas and that the patient should speak with his or her oncologist and/or primary care provider for related concerns. Include a list of local and national resources to assist the patient in obtaining the proper services
A general statement emphasizing the importance of healthy diet, exercise, smoking cessation, and alcohol use reduction may be included. Statements may be tailored if particularly pertinent to the individual

This information is available at www.facs.org/publications/newsletters/coc-source/special-source/standard33.[43] For the ASCO SCP templates and other survivorship resources, visit www.asco.org.

new issues that must be dealt with for successful implementation.

Since the 2006 IOM report, the rapid development of health information technology has increasingly fostered the ability to deliver value-based cancer care.[11] To that end, the Health Information Technology for Economic and Clinical Health (HITECH) Act of 2009 promotes the adoption and meaningful use of EHRs. Based on data from the American Hospital Association, 85% of acute care hospitals had certified EHRs that met Federal requirements for meaningful use by 2012, with variation by state.[12] This current adoption of EHRs is a dramatic increase from 9.4% in 2008.[12] An important aspect of use will be the interoperability among EHRs to allow data exchange in a meaningful way. Here is where the SCP will be critical as an important tool for care coordination and in sharing a concise history of patient diagnosis, summary of treatments received, surveillance plan, and management of the consequences of cancer and its treatment.

One component of valuable EHRs is the ability to have oncology-specific clinical decision support systems [CDSS] that draw on created knowledge bases and patient data, which have the potential to tailor decisions across of the cancer continuum.[11,13] CDSS have rules, alerts, and workflow tools that can be used for the development of SCPs. This includes the integration of CPGs, such as surveillance recommendations with patient data to create the SCP. Other ways

to enhance the quality of cancer care using the SCP could include the addition of patient-reported outcomes (e.g., if a symptom is reported, information about that symptom and ways to manage it could be incorporated into the SCP). Other opportunities to improve care would include data mining and research.[13] However, we are still in the nascent period of using EHRs to develop and deliver SCPs and have yet to realize the full possibilities for improving the quality of survivorship care. Many practices are currently working with EHR vendors to implement SCPs, so we will be learning many lessons about what works and what does not along the way. One can use Donabedian's conceptual framework, as described in Table 1, using structure, process, and outcomes to consider issues of EHRs implementation of the SCP.[14]

Structure

One must decide what elements to include in an SCP. There are a number of free-standing, independent templates (e.g., Journey Forward, LIVESTRONG) that have been used, but they have operability issues within EHRs. ASCO recently reviewed and revised the essential elements to include in an SCP.[15] These elements, endorsed and adopted by the CoC, can be identified or created within a template to be auto-completed or to provide standard options for completion within any EHRs (Table 2). Where these documents will be stored within EHRs, how they can be shared with intended users (survivor, primary care provider, and other relevant providers), and how they can be tracked and reported are other structural issues that need to be resolved.

Process

A number of process issues need to be addressed (see sidebar). These decisions need to be discussed, decided, tried, and revised based on experience with the stakeholders of this process. Furthermore, how these issues are addressed may vary by type and size of oncology practices.[16,17] Effective change management is needed and includes engaging key stakeholders, standardizing terminology, clinical practices, and processes.[16] Articulating and agreeing on key assumptions help guide the approach and assure that this process, and ultimately the document, is patient and primary care centered. This process should be standardized as much as possible but should allow for variations to reflect the complexity of cancer care. It is helpful to have at least one champion and to work with an interested and willing early-adopter group to pilot this process.[18]

Implementation of this process will take time and require flexibility until the system for developing and delivering SCPs becomes standardized and incorporated into practice. For example, in a large academic medical center, there may be a number of disease-specific groups with differing approaches about who sees the patient and how often. Decisions about who completes and delivers the SCP when all three treatment modalities are delivered versus when one is delivered could vary. For example, these decisions could fall on the last person who treats the patient or the first person

SIDEBAR. Questions to Consider When Implementing Survivorship Care Plans within an Electronic Health Record

1. How will eligible patients be identified and tracked?
2. How will a provider know when an eligible patient is due to receive a survivorship care plan (SCP)?
3. How will the SCP be created and by whom?
4. How will a provider know when to deliver the SCP?
5. How will the SCP be delivered to the patient and primary care provider and be documented?
6. How will you bill for this service?
7. Where will it be stored within the electronic health record for others to access?
8. How will you track the number of SCPs developed and delivered?
9. How will you monitor and evaluate your effectiveness in achieving the Commission on Cancer's goals for your cancer program?
10. How will this effort become a sustained standard of care?
11. Will you collect any patient/provider outcome measures related to the SCP?

who sees the patient during the first follow-up visit. To say that the devil is in the details is an understatement in trying to delineate and implement a new process such as this. The good news is that one is not trying to undo a previous way of implementing the SCP—this is a new endeavor.

Another important questions about the process is how is it delivered once it is completed. The SCP is a paper document and it does not serve the original intent by merely handing it to the patient and checking off that it was delivered. The SCP is meant to serve as a communication tool to facilitate review of the patient's diagnosis and treatment, guide discussion of planned surveillance and who will be responsible, and encourage identification and discussion of any current or future concerns or issues the patient may face post-treatment. In one study in patients with colon cancer, the delivery of the SCP did not lengthen the usual surveillance visit, but it did provide structure to what was discussed.[19] Nutritional concerns and bowel management problems quickly became identified as issues most of these patients raised, and these topics were then incorporated routinely into the SCP and visit.

There are many barriers to SCP implementation and these need to be addressed as they are identified. Working closely with the EHR vendor during the development and piloting phase is critical. Receiving input from anticipated users and having them try to use the SCP EHR system as intended will identify many issues with implementation. Answering the questions in the sidebar can be time consuming, and the approach may need to change over time with experience. One of the critical issues is reimbursement for SCP completion. As of January 1, 2015, SCP preparation can be billed as a new CPT code, 99490 (chronic care management services, at least 20 minutes of clinical staff time directed by a physician or

TABLE 3. Representative QOPI Survivorship Questions

Question	No. of Practices
Chemotherapy treatment summary completed within 3 months of chemotherapy end?	310
Smoking/tobacco use cessation administered appropriately in the past year?	313
Infertility risks discussed prior to chemotherapy?	181
Fertility preservation options discussed, or referral to specialist?	181
Imaging or tumor marker within 12 months after breast cancer diagnosis in patients treated with curative intent?	111
Complete family history documented for invasive breast cancer?	98
Genetic testing for invasive breast cancer?	95

Abbreviation: QOPI, Quality Oncology Practice Initiative.

other qualified health care professional per calendar month) to describe chronic care management.[20] This may help overcome the barrier of completing an unfunded mandate. Visits in which the SCP is delivered can be billed as appropriate for the visit.

Outcomes

A barrier to adoption has been the minimal amount of evidence demonstrating benefits for SCPs.[21] Receiving an SCP from an oncologist is associated with primary care providers reporting always or almost always discussing recommendations and delineation of provider responsibility with survivors (OR 9.22; 95% CI, 5.74 to 14.82; p < 0.001) compared to primary care providers reporting receiving SCP less than always or almost always from the oncologist.[22] Immediate outcomes may include increased knowledge about surveillance plans and satisfaction with care, while longer-term outcomes may include increased adherence to surveillance plans, with decreased undertesting and overtesting and identification and management of long-term effects. Other provider level

and system level outcomes might also be included. Ongoing studies eventually may demonstrate SCP effectiveness; regardless, the SCP is a requirement in the ACoS CoC Cancer Program Standards, and it is an ASCO QOPI measure and needs to be incorporated into cancer care. Based on stakeholders perspectives, SCPs have been positively viewed and, at a minimum, may enhance patient and primary care provider satisfaction of care with the oncology team.[8,23]

LESSONS FROM THE ASCO QOPI SURVIVORSHIP MEASURES

In addition to the dissemination of oncology CPGs by groups such as ASCO and the NCCN as a means of improving the quality of cancer care, it is essential to evaluate whether these recommendations influence physician practice. To this end, the ASCO QOPI project began in 2006 with the goal of measuring how well physician practices adhere to quality measures over time.[24] In 2013, data from 156 academic and community practice groups representing 2,100 physicians from different regions of the country was published.[25] Overall, adherence to standard of care and guideline recommendations improved over time in certain domains (e.g., testing for *KRAS* mutations in colorectal cancer when using targeted treatment), whereas end-of-life care and symptom/toxicity management remained static.[25] Thus, the QOPI is an effective tool to measure physician behavior and adherence to guidelines over time.

Several core QOPI survivorship measures that are based on guideline recommendations have been defined, including whether the patient received a summary of cancer treatment,[15] tobacco cessation referral,[26] counseling about infertility risks and fertility preservation options,[27] whether tumor markers/imaging tests were done within 12 months of completing treatment,[28,29] and the completion of a family history and genetic testing for invasive breast cancer.[30,31] Depending on the specific question asked (Table 3), between 95 and 313 medical practices contributed data in the form of medical re-

FIGURE 1. Chemotherapy Treatment Summary Completed within 3 Months of Chemotherapy End (310 Practices)
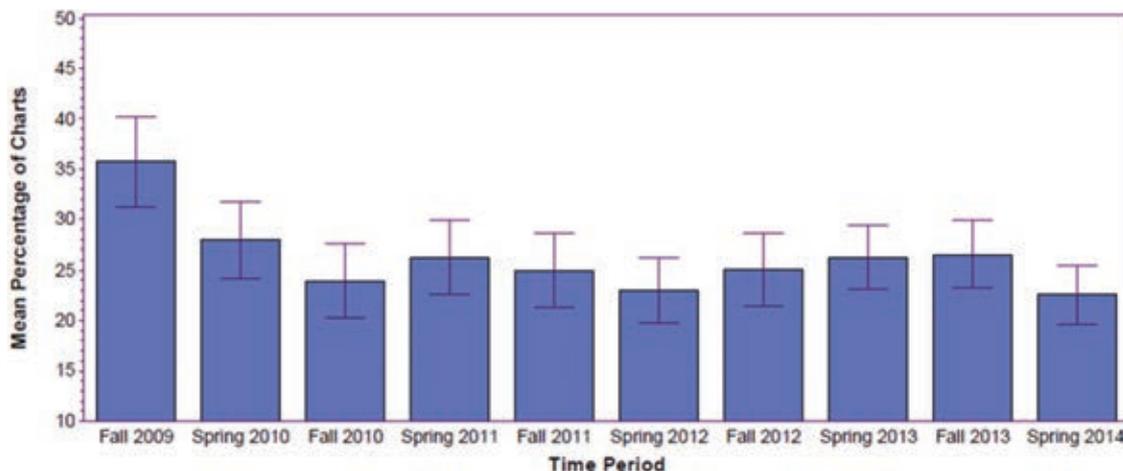
FIGURE 2. (A) Infertility Risks Discussed before Chemotherapy (181 Practices); (B) Fertility Preservation Options Discussed or Referral to Specialist (181 Practices)
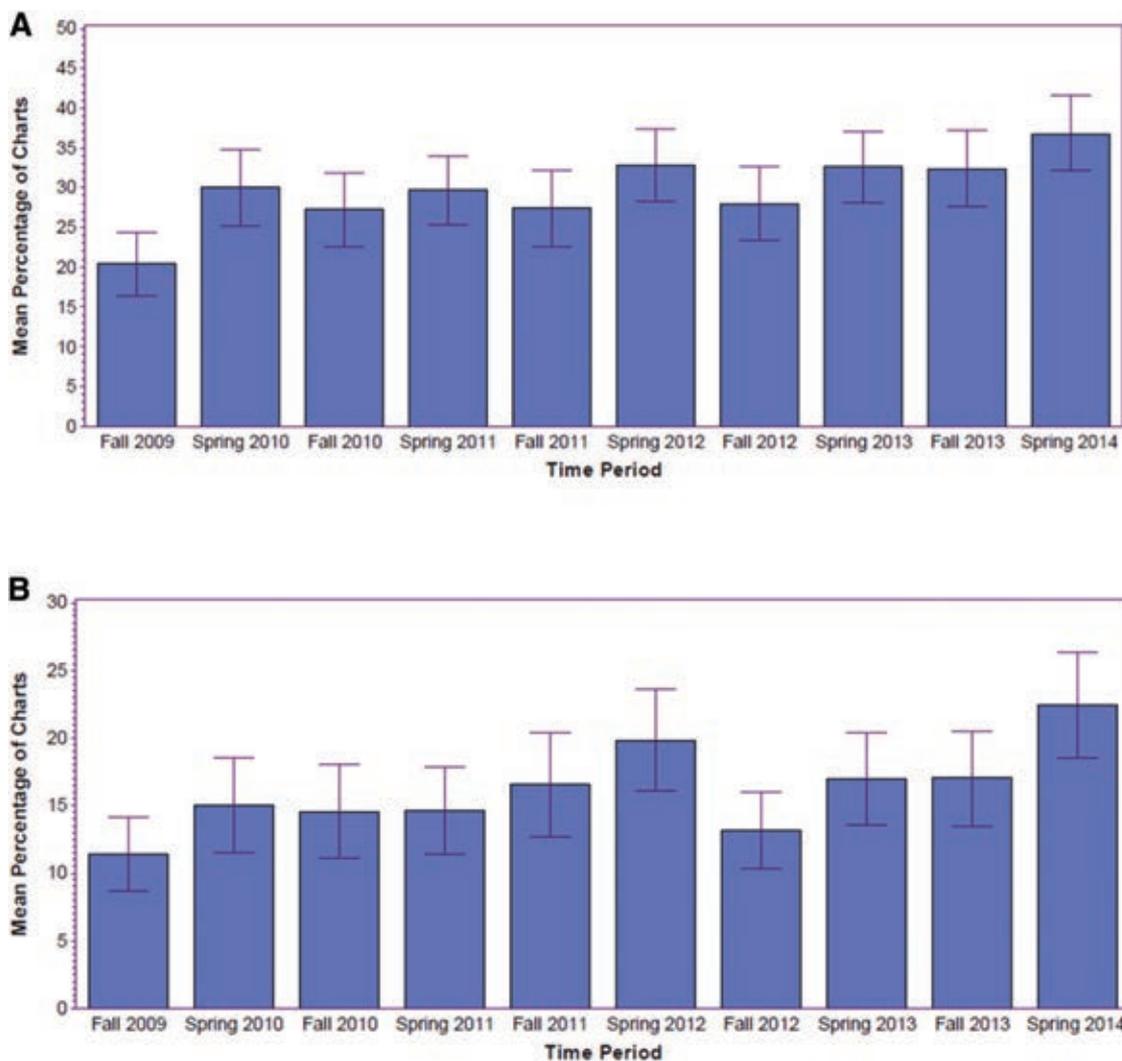
cords. The selected QOPI survivorship measures to assess physician adherence to these guideline recommendations are discussed below.

Treatment Summary

The development and implementation of the SCP has been described earlier in this article, and the QOPI effort to document uptake of this recommendation to provide a treatment summary within 3 months of completing treatment is documented in Fig. 1. The percentage of physician practices in which a treatment summary is documented decreased from 35% in 2009% to 20% in 2014. However, recent initiatives to simplify the ASCO SCP, along with extensive efforts to assure integration of the SCP with electronic medical records, and the requirement of the CoC that by January 2019 all individuals receive an SCP should begin to reverse this decreasing trend.[7] However, to be successful, the barriers previously described will need to be addressed.

Tobacco Cessation

In 2003, ASCO released a policy statement on tobacco cessation,[32] and an update was published in 2013.[26] A cornerstone of this policy is that every individual should be queried about smoking status, and appropriate interventions and referrals to smoking cessation programs should be undertaken. There were consistently 81% to 84% of medical records that documented a smoking/tobacco cessation discussion in the years 2009 to 2014. Although guideline adherence is consistently greater than 80%, one wonders whether that goal should be higher.

Risk of Infertility

The ASCO clinical practice guideline on fertility preservation was published in 2006 and recently was updated in 2013.[27] Among the key recommendations were to discuss fertility preservation with all individuals of reproductive age and to refer those interested in fertility preservation to reproductive

FIGURE 3. Imaging or Tumor Marker within 12 Months of Completed Treatment with Curative Intent (111 Practices)
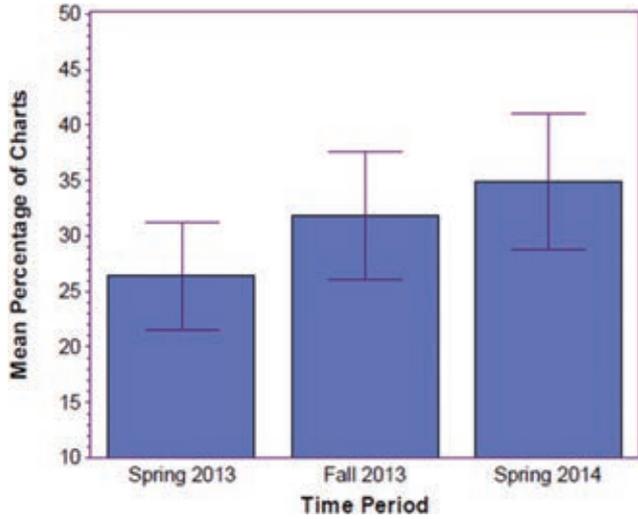
specialists. Figs. 2A and 2B show the improvement over time during the period 2009 to 2014. A discussion about the infertility risk before chemotherapy increased from 20% to 35%. Likewise, fertility options discussed or referred to a specialist increased from 11% to 24%. These increases over time may represent a validation of the QOPI process. However, these rates are overall low and highlight the need for improvement.

Imaging or Tumor Markers within 12 Months of Completing Treatment

First in 2006[28] and updated in 2013,[28] the ASCO guideline on breast cancer follow-up care states that imaging studies or tumor markers are not recommended in asymptomatic women with breast cancer who have completed treatment with curative intent. The percent of medical records that document imaging or tumor markers within 12 months of completing treatment with curative intent actually increased from 25% to 35% over 1 year (Fig. 3). Although there a too few data points to establish a convincing trend, the fact that even 25% of medical records document tests that are not ben-

FIGURE 4. (A) Genetic Testing for Invasive Breast Cancer (95 Patients) (B) Complete Family History Documented for Invasive Breast Cancer (98 Patients)
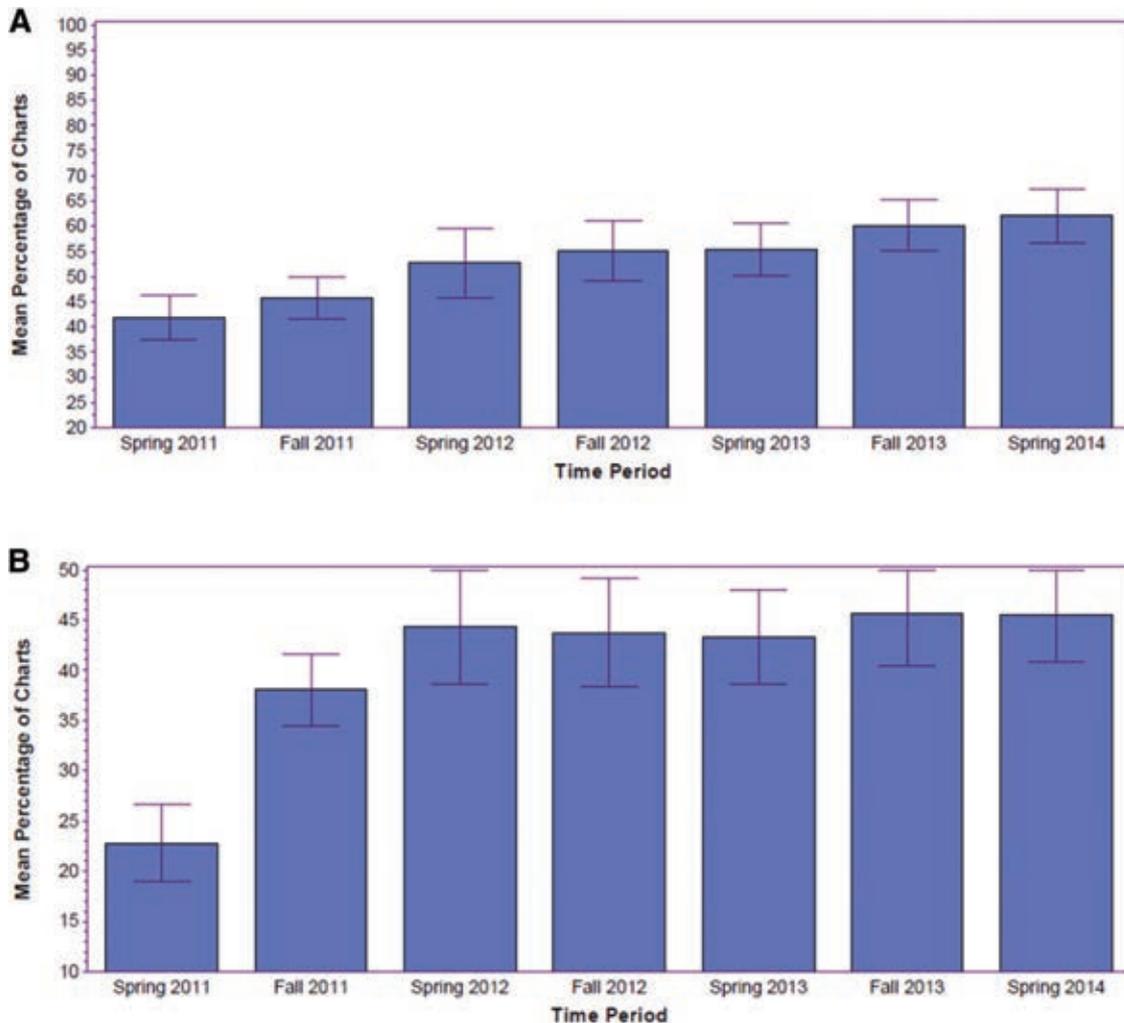
eficial suggests that current guidelines are not effectively reaching and/or influencing physicians who care for these women.

Genetic Testing and Family History

In 1996, 2003, and 2010,[31,33,34] ASCO provided a policy statement with recommendations for genetic testing. In 2014, ASCO issued an expert statement recommending the minimal family history for individuals with cancer.[30] Penetration into practice is evidenced by a steady increase in genetic testing of women with breast cancer (Fig. 4A), as evidenced by the QOPI data. In contrast, only 45% of medical records documented complete family histories in women with breast cancer (Fig. 4B).

QOPI was developed as a tool to measure quality of cancer care over time by providing a mechanism to assess physician adherence to guidelines.[24,35] It has several strengths, including that it draws from a mix of academic and community practices throughout the country. However, there are also several limitations, including reporting data from only those practices that participate in QOPI and reliance on what is and what is not documented in the medical record.[25] In addition, QOPI does not capture the complexity of patient care when

the clinical and psychosocial situation requires an exception to following practice guidelines. Nonetheless, QOPI is one of the very few ways in which the quality of survivorship care is being measured.

QOPI data highlight another important area that deserves mention. Tremendous time and effort has produced 50 ASCO guidelines and expert statements[36] and 20 years of NCCN practice guidelines.[37] Much less time has been devoted to evaluate the best methods of disseminating guidelines and increasing adherence to guideline recommendations. There are conceptual frameworks,[38-40] randomized trials,[41] and systemic reviews evaluating various interventions; the vast majority have non–cancer-related guidelines.[42] Efforts should be directed toward developing more effective ways to disseminate guideline recommendations and toward developing additional tools to measure quality.

In summary, as the scientific evidence base to guide cancer survivorship care grows, the role of guidelines to translate evidence into practice and metrics to assure that quality, or the lack thereof, is measured will become increasingly important. This will need to occur at both the individual practice level and the system level. Much is to be done, and we've only just begun.

Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

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PATIENT AND SURVIVOR CARE

The Challenges of Pain Management

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Cancer Pain Management: Safe and Effective Use of Opioids

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OVERVIEW

Pain remains a serious consequence of cancer and its treatment. Although significant advances have been made in providing effective cancer pain control, barriers persist. Lack of knowledge, limited time, financial restrictions, and diminished availability of necessary medications serve as significant obstacles. Safe and effective opioid use in a patient with cancer requires skill to overcome these challenges. Understanding the mechanism of action, along with the pharmacokinetics and pharmacodynamics, of opioids will lead to appropriate selection, dosing, and titration of these agents. Rotation from one opioid or route to another is an essential proficiency for oncologists. As opioid-related adverse effects often occur, the oncology team must be expert in preventing and managing constipation, nausea, sedation, and neurotoxicities. An emerging concern is overtreatment—the excessive and prolonged use of opioids in patients when these agents may produce more harm than benefit. This can occur when opioids are used inappropriately to treat comorbid psychologic issues such as anxiety and depression. Recognizing risk factors for overuse along with key components of universal precautions will promote safe use of these medications, supporting adherence and preventing diversion, thereby protecting the patient, the prescriber, and the community. Because substance use disorders are not rare in the oncology setting, attention must be given to the balance of providing analgesia while limiting harm. Caring for patients with substance misuse requires compassionate, multidisciplinary care, with input from supportive oncology/palliative care as well as addiction specialists.

Pain is a serious consequence of cancer and its treatment. Although great strides have been made in increasing awareness of the need for effective cancer pain control, barriers persist that lead to undertreatment.[1-3] Health care professionals' lack of knowledge (despite extensive efforts to improve education), limited access to specialists, and diminished availability of necessary medications are significant obstacles. Insufficient time, resulting from increased demands to provide care for more patients during shorter visits, along with expanding requests for documentation, insurance authorizations, and other regulatory requirements, complicates delivery of comprehensive pain control.[4,5] Balancing these demands has proven challenging, and excellent pain control can suffer as a result.

Awareness of the safe and effective use of opioids in the oncology setting is essential to the provision of adequate pain relief. Understanding the mechanism of action, along with the pharmacokinetics and pharmacodynamics of opioids will lead to appropriate selection, dosing, and titration of these agents. As adverse effects often occur, the oncology team must be skilled in preventing and managing constipation, nausea, sedation, and neurotoxicities. An emerging concern is overtreatment with opioids—the excessive and prolonged use of opioids in patients when these agents may produce more harm than benefit. This can occur when opioids are used inappropriately to treat comorbid psychologic issues such as anxiety and depression. Recognizing risk factors for overuse along with key components of universal precautions will promote safe use of these medications, protecting the patient, the prescriber, and the community.

PRINCIPLES OF OPIOID USE

Opioid analgesics have been the most useful group of drugs for the management of severe pain for more than 200 years.[6] All opioid analgesics work mainly by binding the Mu opioid receptors located along the nociceptive pathway. These Mu receptors are found in multiple locations presynaptically and postsynaptically. The direct result of the opioid binding to the receptor is decreased afferent nociceptive neuronal depolarization. In recent years it has become clear that new receptors have multiple subtypes.[7] Different opioid Mu agonists will bind to slightly different subtypes of Mu receptors. This variability and the differences in pharmacokinetic and pharmacodynamic profile explain the frequently observed difference in both analgesic response and side effect to different opioid analgesics. An important pearl for clinicians is that there is considerable interpersonal variation in analgesic response to opioid agonists.

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Choice of Opioid and Initial Opioid Titration

In patients who have never been exposed to opioids before, titration is quite simple. The starting dose is well established for all major opioid analgesics and it is the equivalent to 30 mg of morphine per day orally (20 mg oxycodone, 10 mg of oxymorphone, etc.). The starting dose of an opioid is not driven by the intensity of the patient's pain expression but rather by safety considerations, and therefore, the initiation of opioids is simple and generally very safe. In patients with good renal function and good liver function and who are not receiving other drugs that might interact at the pharmacokinetic or pharmacodynamic level, all opioids are similarly safe and effective.

Opioid metabolism. Opioids undergo phase I oxidation or hydrolysis mainly by the cytochrome 3A4 and 2D6 enzymes, followed by phase II glucuronization that increases their hydro-solubility for renal elimination. Table 1 summarizes some of the metabolic sub-products of the main opioid agonists. It is important to note that the 3A4 cytochrome produces largely inactive metabolites. Therefore, drugs that block 3A4 will increase either the parent compound or the alternative pathway toward active metabolites. Patients undergoing this interaction will develop opioid toxicity—mainly sedation. Agents frequently involved in these interactions for patients with cancer include macrolide and fluroquinolone antibiotics, azoles, HIV antiretrovirals, irinotecan, and many of the new targeted agents. On the other hand, the 2D6 cytochrome pathway produces largely active metabolites, and the blockage of this pathway by drug interactions will result in decreased analgesic effects. This is particularly important in the case of codeine since it does not largely bind to the opioid Mu receptor but requires activation by 2D6 to morphine. The main 2D6 drugs for patients with

Table 1. Phase I Metabolism of Opioids

Drug	Cytochrome	Results
Morphine	None	
Hydromorphone	None	
Oxymorphone	None	
Fentanyl	3A4	Norfentanyl
Oxycodone	3A4	Noroxycodone
	2D6	Oxymorphone*
Hydrocodone	3A4	Norhydrocodeine
	2D6	Hydromorphone*
Codeine	2D6	Morphine*
Methadone	3A4	M1-M2
Tramadol	2D6	Desmethyltramadol*

*Active metabolite.

cancer include some selective serotonin reuptake inhibitor antidepressants and neuroleptics such as haloperidol or chlorpromazine. It is important to remember that 8% to 20% of the population are genetically poor metabolizers at the 2D6 level.[8]

Some opioids have minimal or no phase I metabolism. These include morphine, hydromorphone, and oxymorphone. The likelihood of interactions at the cytochrome level from these opioids is minimal, making these three opioids ideal for patients with liver failure or potential drug interactions. Opioids with no major phase I (morphine, hydromorphone, oxymorphone) and the active metabolites of the other opioids (Table 1) undergo glucuronidation and renal elimination. Some of these glucuronides are active (e.g., morphine-6-glucuronide, glucuronide), and others are not active on the opioid receptor but neurotoxic (e.g., morphine-3-glucuronide and hydromorphine-3-glucuronide). For patients with renal failure, all these opioids should be used with frequent monitoring for neurotoxicity. Methadone is a very good alternative in renal failure since its metabolites are largely inactive and are not eliminated into the urine.

If a patient who has been on a stable dose of an opioid analgesic develops sedation it is important to ask if any new drugs have been added that might affect the pharmacokinetic profile. Also determine if the patient is now in liver or renal failure and if new drugs have been added that might increase the level of sedation of the patient from the pharmacodynamic perspective. These drugs include hypnotics, antihistamines, sedating antidepressants, and anticonvulsants frequently used for neuropathic pain.

Many extended release opioid preparations are available (Table 2). All the opioids in the table have been modified so as to delay absorption from the gut or the skin. Although methadone is not an extended release drug, it can be administered every 12 hours because of its very slow elimination after rapid oral, rectal, or subcutaneous absorption. Extended release opioids are generally not more effective or less toxic than immediate release opioids. Their main advantage is much more comfortable administration that might improve adherence

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KEY POINTS

· Safe and effective control of cancer pain demands thorough knowledge of the pharmacokinetics and pharmacodynamics of opioids that guide dosing, titration, and rotation.
· Prevention and management of adverse effects of opioids requires careful assessment and knowledge regarding agents used to treat these complications.
· Overtreatment of cancer pain can occur when opioids are used to treat symptoms other than pain or dyspnea, including anxiety, depression, or sleep disorders.
· Evaluation of risk factors for opioid misuse, including current or past use of illicit substances, family history of substance use disorder, environmental exposure, along with a history of sexual or physical abuse, guides safe and effective care.
· Universal precautions, including measures to advance adherence and safe storage, will promote safe use of these medications while protecting the patient, the prescriber, and the community.

Table 2. Extended Release Opioids

Drug	Route	Frequency
Morphine	Oral	Every 12 hours
Hydromorphone	Oral	Every 24 hours
Oxycodone	Oral	Every 12 hours
Fentanyl	Transdermal	Every 72 hours
Oxymorphone	Oral	Every 12 hours
Hydrocodone	Oral	Every 12 hours

to chronic treatment for patients as compared to taking immediate release opioids such as morphine, hydrocodone, hydromorphone, or codeine every 4 hours day and night. However, extended release opioids are generally five times more expensive than immediate release opioids, and insurance payers frequently deny payment for these agents.[9] Therefore, the insurance company occasionally may request that patients change opioid analgesic or pay large amounts of money out of pocket. In these cases, chronic management with immediate release opioid is an appropriate alternative.

All patients with chronic cancer pain should be started on regular opioids, ideally using an extended release formulation (Sidebar 1). In addition, patients with cancer pain require access to immediate release opioids for episodes of break-through pain. Each dose should be approximately 10% (ranging between 5% and 20%) of the daily regular opioid dose. Close to 100% of the patients need to be prescribed a regular laxative every day since constipation is a universal and frequently under diagnosed problem. In addition, patients should be prescribed antiemetics since approximately half of the patients started on an opioid agonist will develop nausea for the first 3 days. Metoclopramide is an excellent option because of its combination of central and pro-kinetic effects. After the first 3 to 4 days, nausea is either minimal or absent.

Opioid titration. Even after ideal management, only approximately 50% of the patients will reach their personalized pain goal (3/10) after one visit.[10] Therefore, it is important to either follow up or phone the patient less than 1 week after the initial management to further titrate the opioid dose and to consider adjuvant drugs or drugs for the management of side effects. The minimal clinically important increase or decrease in dose will be approximately 30% of the daily dose. Opioid titration is always conducted as a percentage rather than an absolute number because of the large dose range. For example, a patient coming for follow-up in poor pain control receiving 100 mg of equivalent morphine daily dose will require an increase of at least 30 mg per day. A patient coming with a similar degree of poor pain control but receiving a dose of 300 mg of equivalent morphine per day will require an increase of approximately 100 mg per day.

When calculating the daily morphine equivalent dose, ask the patient how many extra opioid doses they received per day. For example, a patient started on 15 mg of extended release morphine every 12 hours and 7.5 mg of immediate release morphine orally every 4 hours as needed. One week later the patient complains of pain 8/10. The patient is receiving four immediate release doses per day. Total morphine equivalent dose for this patient is regular daily dose 30 plus breakthrough pain 30, making a total daily dose of 60 mg. An appropriate increase for this patient would be approximately 30% to 50% of the daily dose (20–30 mg). Therefore, the new regular opioid dose should be approximately 90 mg/day (either 30 mg every 8 hours or 45 mg every 12 hours). The new extra dose will need to be approximately 9 to 10 mg every 4 hours as needed since the ideal extra dose is approximately 10% of the daily dose.

Opioid rotation. Approximately 80% of patients with cancer will need at least one change in the type of opioid. The main reasons for opioid rotation are the development of opioid induced neurotoxicity or lack of appropriate pain control after appropriate dose titration. Sidebar 2 summarizes the main clinical features of patients who develop opioid-induced neurotoxicity. Whenever patients develop clinical findings—including a combination of sedation, myoclonus, hyperalgesia either localized at the area of the existing pain or generalized cutaneous hyperalgesia, or elements of delirium (confusion, inattention, disorientation, hallucinations, psychomotor agitation)—an opioid rotation should be conducted. Opioid rotation works by eliminating the offending drug, and it is more important to make the diagnosis of opioid-induced neuro-

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Sidebar 1. Ideal Initial Management of Chronic Pain Due to Cancer

· Extended opioid regularly (oral or transdermal)
· Immediate release opioid for breakthrough pain, orally (10% of the daily dose)
· Laxative regularly and titrate to normal frequency before cancer (e.g., senna, polyethylene glycol)
· Antiemetic available for all patients upon initiation or dose increase (metoclopramide)
· Consider adjuvant drugs
· Follow up by telephone or in person in approximately 1 week

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Sidebar 2. Clinical Findings in Patients with Opioid-Induced Neurotoxicity

· Sedation
· Myoclonus
· Hyperalgesia (localized or generalized)
· Hallucinations
· Psychomotor agitation
· Confusion

toxicity and proceed to change the type of opioid than which new opioid the patient is rotated to.

The total morphine equivalent daily dose of the current opioid is determined by adding the regular and all breakthrough pain doses for the past 24 hours. This dose can then be translated into the dose of the new opioid using dose ratio tables. For example, for a patient receiving a total daily dose of morphine of 300 mg per day, the equivalent daily dose of oxymorphone could be approximately 100 mg per day, for oxycodone 200 mg per day, etc.

There is considerable interpersonal variation in the opioid dose ratio, and therefore, frequent follow-up after conducting an opioid rotation is important. Opioid rotation is safe for most opioid agonists since most patients develop a significant level of cross-tolerance. Since cross-tolerance to sedation and respiratory depression is not complete, in most cases, the opioid rotation is conducted by reducing the dose of the new opioid by 30% to 50%.

One of the most remarkable exceptions to this rule of cross-tolerance is methadone.[11] Methadone is one of the most exciting opioid analgesics because of its ability to control pain that has been refractory to multiple other opioids, its lack of active toxic metabolites, its long half-life that allows for administration once or twice a day, and its very low cost that makes it affordable for low-income patients or those who are uninsured. However, methadone also has significant 3A4 cytochrome interactions and can be dangerous for opioid rotation because of its lack of cross-tolerance with all other Mu opioid agonists. For this reason, only experienced clinicians should conduct opioid rotations to methadone.

Opioid Side Effects

Adverse effects to opioids are common and should be assessed regularly (Table 3). The vast majority of patients will need regular laxatives. The most commonly used include senna and polyethylene glycol. These laxatives should be given daily, and patients should be instructed to self-titrate

Table 3. Opioid Side Effects

Common
Sedation
Constipation
Nausea
Less Common
Opioid-induced neurotoxicity (Sidebar 2)
Sweating
Urinary retention
Pruritus
Adult respiratory distress syndrome
Addiction
Respiratory depression
Hypogonadism

the dose of laxative until they have bowel movements of the same frequency and volume as they had before the diagnosis of cancer. Patients will quite commonly underestimate their level of constipation since their intake is less, they are less physically active, and they may assume constipation as "normal." The addition of an opioid can lead these patients to severe cases of obstipation, emesis, abdominal pain, anorexia, and even bowel perforation. Universal precautions regarding education and management of constipation are required whenever an opioid analgesic is prescribed.

Nausea is a frequent side effect during the initiation of opioids but is much less frequent during titration or opioid rotation. Preventative antiemetics including metoclopramide can be very useful.

Sedation is also a frequent side effect of opioid initial titration or opioid rotation. In patients who develop persistent opioid sedation, methylphenidate has been shown to reduce this side effect and allow patients to function better.[12] Methylphenidate can be used intermittently for the first few days after each dose change, and it can also be used as needed so patients can self-titrate during daytime.

Respiratory depression is rare but life threatening. It may result from excessive dose, patient chemical coping, drug or active metabolite accumulation from renal or liver failure, pharmacokinetic changes from drug interaction, or pharmacodynamic effects when combined with alcohol, benzodiazepines, and other sedatives.

As previously noted, neurotoxicity is the most dramatic side effect of opioid analgesics. Delirium occurs in more than 85% of patients with cancer at some point before death, and opioids might be a contributor in these patients, so it is important to conduct early opioid rotation. There are also multiple other causes for delirium in patients with advanced cancer, and delirium will ultimately occur in the vast majority of patients with cancer before death, even when they are not receiving any opioid analgesics.

SCREENING AND MANAGING OPIOID OVERTREATMENT, MISUSE, AND ABUSE

An emerging challenge to safe and effective cancer pain control is overtreatment with excessive and prolonged use of opioids in patients when these agents may produce more harm than benefit. Many of the same barriers that have contributed to undertreatment, such as lack of knowledge, time, and reimbursement, have advanced opioid overuse. As a result of these obstacles, comprehensive pain assessments are not conducted, and referrals for mental health counseling or physical therapy are not provided because these treatments are frequently not compensated by third-party payers. Seemingly, the provider may believe the only option is to prescribe an opioid.

Although limited data exist in the oncology setting, strong support for opioid overutilization comes from the treatment of pain in chronic nonmalignant pain settings. Higher doses of opioids in this population are often associated with mental

Table 4. Factors that Place Individuals at Risk for Overtreatment with Opioids

Long-Term Survival
Comorbid Mental Health Conditions
Anxiety
Depression
Sleep disorders
"Chemical copers" or those with limited coping skills
Limited or No Financial Resources
Pre-Existing Substance Use Disorders

Table 5. Potential Reasons for Aberrant Drug-Taking Behavior

Pseudo-addiction (Inadequate Analgesia)
Amount of drug ordered (e.g., dose, number of tablets) too low
Insurance limits prevent adequate supply
Pharmacy shortages diminish availability
Psychiatric Conditions
Mood disorders (e.g., anxiety, depression)
Encephalopathy or cognitive disorders
Inability to Follow Treatment Plan
Low literacy
Misunderstanding regarding "prn"
Substance Use Disorder
Criminal Intent

health conditions such as anxiety or depression, along with substance use disorders.[13] Emerging data suggest that prolonged use of opioids leads to hypogonadism, fractures, and cognitive blunting.[14] Provocative data from the laboratory suggest opioids may accelerate tumor growth.[15] Finally, in some patients, opioid use is not leading to improved function or quality of life— essential goals for those with chronic non-malignant pain and long-term cancer survivors.

Risk Factors for Overtreatment

Providing effective pain control should include consideration of factors associated with risk for overtreatment (Table 4). The cancer and/or its treatment may have resulted in persistent pain, the uncertainty of recurrence can be associated with significant anxiety or depression, and limited coping strategies along with reduced financial resources (sometimes a consequence of cancer treatment and/or losing one's job) all contribute to a state of great distress.[16] Coupled with a history of substance use disorder, the patient may conclude that opioids may be the most appropriate, or only, solution.

To avoid labeling, when apparent aberrant behavior occurs, the oncology team must carefully reflect on alternate explanations (Table 5). Is the patient calling frequently for refills because he or she is not getting an adequate supply of medications, because either our orders are insufficient or the insurance company has a ceiling on the dispensed amount of tablets at a number too low to meet the need? Or is the patient overwhelmed with trying to understand when to take a drug "prn" or "as needed," and they default to every 3 hours, regardless of their pain intensity? Or is the patient selling the medication to purchase other powerful illicit agents or to feed their children?

Universal Precautions

To provide safe and effective pain care, experts suggest implementing universal precautions. These measures are considered universal because we cannot predict who has a substance use disorder. These precautions employ screening, agreements, and adherence monitoring strategies.[17] Comprehensive assessment of the current and past use of legal (e.g., tobacco, alcohol) and illicit substances (e.g., prescription drugs obtained from family or purchased illegally) is

warranted. Cannabis use should be specifically evaluated, as many do not consider it to be illicit, particularly as more states are legalizing its recreational or medical use. Screening tools, such as the CAGE questionnaire, can be used to complement this assessment by determining the extent of harmful behaviors. Substance use disorders are not rare in the oncology setting.[18,19]

Agreements, formerly called contracts, detail both the patient's and provider's responsibilities in managing pain.[20] Key components generally include the requirement to use one prescriber and one pharmacy along with the condition that any changes in the plan must first be discussed. These agreements also clarify how the patient can contact the provider or their team and the expected frequency of clinic visits. Safe storage and handling of medications may be included to prevent diversion and community exposure to controlled substances. There are limited data regarding the efficacy of these agreements in the oncology setting.

Adherence monitoring strategies include the use of pill counts, prescription monitoring programs, and urine toxicology screening. Pill counts can be performed in the clinic to determine appropriate use of an opioid or other medication by comparing the number of pills remaining with what might be expected. Complementing this information is the regular use of prescription monitoring program records. Forty-nine states currently provide databases that inform prescribers about the dispensing of controlled substances. Although the information provided among states varies, using a patient's name and date of birth, the prescriber can determine the drug, date it was dispensed, dose, number of tablets, name of prescriber and pharmacy, and payment method (i.e., self-pay versus third-party payer). This informs safe prescribing but also assists when seeing new patients with low health literacy who do not know the name or dose of their medication.

Random toxicology screening can tell the prescriber whether the drug ordered is present and if nonprescribed substances have been ingested.[21] Most screening is conducted using urine, as it is less invasive and more cost-

effective. Basic screens use immunoassay to ascertain the presence of certain classes of substances (or their metabolites), with most including opioids, amphetamines, benzodiazepines, barbiturates, cocaine, phencyclidine, and tetrahydrocannabinol. If findings are abnormal, more elaborate and expensive testing can be performed to determine the presence of specific agents (e.g., oxycodone or morphine) using gas chromatography-mass spectroscopy. Caution is warranted when interpreting findings as false negatives and positives can occur. For example, screens may be negative for opioids when patients are appropriately using fentanyl patches, as fentanyl is often missed by immunoassays. Additionally, patients who are supposed to be taking hydrocodone might have a urinary drug screen positive for hydrocodone, hydromorphone, and morphine since the liver metabolizes hydrocodone into these substances.

An essential component of universal precautions is education about safe storage and disposal of controlled substances.[22] Unfortunately, the majority of patients are unaware of the importance of these measures.[23] One of the most common sources of prescription opioids for abuse is family members and acquaintances. Unfortunately, in the case of patients receiving high doses or opioids, one single tablet taken by an opioid-naive relative or acquaintance can result in death. Since these drugs are frequently called "painkillers," relatives or acquaintances with a minor pain who are opioid naive may ask the patient to share a tablet, and patients should be warned about the danger of this practice.

Substance Use Disorder: Addiction and Chemical Coping

Addiction and chemical coping can occur in patients receiving opioids for cancer pain. By binding to the receptors in the limbic system, opioids not only have an analgesic effect but also produce reward. Patients at risk for opioid misuse will become dysphoric if they do not receive escalating doses. Patients' use of opioid in an effort to manage emotional distress rather than purely physical pain has been defined as chemical coping. This syndrome is more common among young, male patients with a history of alcoholism, drug abuse, and smoking.[24] Patients who rapidly escalate the opioid dose, frequently complain of pain with intensity of 10/10, or are at risk for chemical coping should be referred to a supportive care/palliative care team for interdisciplinary management of this complex problem. Collaboration with addiction specialists may be useful.

One might consider the phenomenon of opioid misuse as a continuum with chemical coping being an early stage of substance use disorders. In our clinical experience, when patients use opioids to treat anxiety, depression, or sleep disorders, these actions can often be countered with compassionate use of motivational interviewing to assist them in gaining insight into their behaviors and to appropriately treat their emotional distress. Early identification is necessary.

Patients with ongoing, untreated substance use disorders, such as regular use of heroin or other illicit substances, re-quire more complex care than can usually be provided in an oncology setting without significant interdisciplinary support.[25] The goal may be the provision of pain control while employing "harm reduction"—preventing diversion of substances to the community while providing safe and effective care. A week's supply of opioid may be prescribed, rather than 1 month, and frequent urine screening may be employed. Interdisciplinary care is warranted.

People with a past history of substance use disorder and those who are in recovery may present a unique challenge. Fears of relapse when presented with an opioid for the treatment of cancer pain may lead the patient to refuse these medications. Thoughtful discussions about using these opioids, trying nonopioid analgesics, employing interventional therapies, and incorporating the patient's sponsor or case manager can be helpful to provide effective relief while limiting the risk of relapse.

A number of new opioid preparations are currently aimed at reducing the risk of illegal use.[26] The idea behind their formulation is that many abusers tamper with tablets to facilitate intranasal or intravenous administration since these routes result in a more rapid peak serum level and a feeling of euphoria. All these preparations consist of an extended release opioid agonist (morphine, oxymorphone, oxycodone, or buprenorphine) modified in one of three different ways: (1) introducing barriers to crushing, chewing, or dissolving; (2) adding an aversive substance that will cause irritation if inhaled, injected, or chewed; and (3) adding an opioid agonist, such as naloxone or naltrexone, that will not be absorbed if the tablet is taken orally as prescribed but will reduce the opioid effect or result in withdrawal if inhaled, injected, or chewed.

These preparations are now in different levels of approval in the United States and other countries. Although they may help reduce the intravenous injection of extended release opioids and perhaps reduce overdose mortality, these preparations will not be able to avoid the two most common sources of chemical coping: taking more than the prescribed dose of intact tablets, and using the immediate release rescue opioid aberrantly. These preparations are also likely to dramatically increase financial toxicity for patients who already face difficulties paying for opioids.

SUMMARY

Safe and effective opioid use in patients with cancer requires balance and skill. These skills include comprehensive assessment, understanding the pharmacokinetics and dynamics of these agents, and knowledge of dosing, titration, and rotation. Balance speaks to the awareness that opioids might be misused, either inadvertently by patients who note they fall asleep or feel less anxious when using these drugs, or purposefully by those with substance use disorders or criminal intent. Universal precautions can support adherence and prevent diversion. Caring for patients with misuse requires interdiscplinary care, with input from supportive oncology/palliative care and addiction specialists.

Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

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PEDIATRIC ONCOLOGY

Real-Time Molecular Genetic Profiling: The Future Is Now (Or Is It?)

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State of the Art Discovery with Tumor Profiling in Pediatric Oncology

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OVERVIEW

It is an exciting era in pediatric oncology with the advent of new technologies to comprehensively characterize cancer genomes in childhood tumors. Defining the genetic landscape of pediatric tumors has not only provided critical insight into tumor evolution, but it has also offered promise for more effective treatment in some cases, such as Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL) and anaplastic lymphoma kinase (ALK)-mutated tumors. However, several challenges remain as the field of genomic tumor profiling emerges. This new technology is costly, and the overall impact on survival has yet to be determined. Tumor heterogeneity and clonal evolution have also presented challenges in the development of targeted therapy. In this article, we review breakthroughs in gene sequencing methodology and discuss examples where genomic discoveries have resulted in the recognition of tumor susceptibility as well as incorporation of targeted therapy. We also discuss how broad scale comprehensive tumor analyses have demonstrated the convergence of individual genetic alterations on common relevant pathways. Although the impact of tumor profiling is best studied within the context of rigorously designed clinical trials, there is promise that there will be growing opportunities for the adaption of precision medicine in pediatric oncology in the future.

The Human Genome Project and technical breakthroughs in gene sequencing methodologies have ushered in unprecedented discoveries into the origins of human cancer. More than 10,000 human tumors have been profiled at the genetic and epigenetic level, and this information has been translated into remarkable improvements in therapy for a minority of cancers where the underlying genetic lesion/pathway can be targeted with specific agents. Most of these examples come from adult cancers, most notably in *BRAF*-mutated melanoma that can be treated with inhibitors like vemurafenib and, more recently, for the small percentage of adults with non-small cell lung cancer that contain *ALK* rearrangements that can be targeted with crizotinib (originally designed as a C-MET inhibitor). However, even before application of high-throughput sequencing, the promise of personalized or precision medicine was realized in the treatment of pediatric Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) with the tyrosine kinase inhibitor imatinib.[1]

Currently, precision medicine has the potential to improve outcome and decrease side effects for already curable pediatric cancers, either in conjunction with chemotherapy or by replacing some conventional agents (e.g., most ALLs, lymphomas, and low-/intermediate-risk solid tumors) and may finally lead to better outcomes for children with high-risk tumors where progress has been either slow or stalled (e.g.,

metastatic solid tumors, advanced neuroblastoma, many brain tumors, acute myeloid leukemia and relapsed disease).

Although there is no doubt that there has been a great success in terms of basic science discovery, there are many practical biologic, technical, and financial hurdles that are likely to interfere with successful full-scale deployment of this strategy for routine treatment of pediatric patients with cancer.[2,3] This review will highlight biologic discoveries in pediatric cancers in the context of changing treatment. The focus will be on current opportunities as well as those on the horizon. This review will specifically focus on targeted therapy in the context of pharmacologic inhibition of a somatically altered gene product or downstream pathway.

NEXT-GENERATION PLATFORMS AND THE COST OF SEQUENCING INDIVIDUAL CANCER GENOMES

Current platforms are capable of performing a variety of sequencing approaches including whole genome (single nucleotide variations and copy number differences in all DNA base pairs), whole exome (mutations and copy number differences in transcribed exons—protein coding, miRNAs, and other RNA species), RNA sequencing (gene expression, splicing changes, fusion transcripts), as well as epigenetic differences using Methyl sequencing (methylation differences in DNA, likely to affect expression) and Chromatin Immu-

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noprecipitation (ChIP) sequencing, which determines chemical changes to the surrounding chromatin that are also likely to affect gene expression. In some cases, data can be produced on an individual in less than a day. Ideally, all platforms would be used to create a full portrait of the genetic and epigenetic landscape of an individual, and there are many examples where combining data (e.g., copy number, gene expression, methylation, and DNA sequencing) shows convergence on alterations in pathways shared among patients of an individual tumor type and/or pathways used by tumor cells to evade therapy. However, the prohibitive cost of sequencing and data analysis now prevents simultaneous deployment of multiple strategies.

The details of these approaches vary but, in general, involve the generation of single-stranded DNA (from genomic DNA, hybridization captured [exome], cDNA [RNA sequencing], bisulfite treated DNA [methyl sequencing] or immunoprecipitated DNA [ChIP sequencing]) with ligation of DNA adapters. Rounds of amplification on beads or glass slides allow adequate coverage of the DNA, and strands can then be sequenced by the sequential addition of fluorescently labeled nucleotides. Varieties of bioinformatic approaches are used to determine quality, align sequences to the genome, and determine variations in sequence. Each approach has advantages and disadvantages. For example, whole-exome sequencing (WES) is less expensive than whole-genome sequencing and focuses on somatic variants in protein coding domains that are likely to contain critical lesions. However, it can miss fusion transcripts and does not provide gene expression information that may highlight activation of biologic pathways.

The sequencing of an individual cancer genome in a short period of time to allow integration into clinical practice is now a reality. However, the cost of a single sequencing run, including analysis and validation, is significant, especially since reimbursement of such assays is still uncertain in many cases. The $1,000 genome has been often quoted as a holy grail for clinical sequencing, and the recent development of the HiSeq X Ten system (Illumina) has finally laid claim to this title. However, achieving this goal requires the purchase of 10 systems costing approximately $10 million and opera-

tion more than 4 years yielding about 72,000 genomes for a total outlay of $82 million in capital and operational costs.[4]

PEDIATRIC CANCER GENOMES AND THERAPEUTIC TARGETS

The practical implementation of precision medicine is facilitated by the identification of somatic changes unique to the tumor that fuel cancer initiation and progression. Moreover, such drivers that are shared among and across tumor types would increase the effect of agents that selectively target the gene product and/or downstream pathway. Although there are a few exceptions, in general, childhood tumors contain far fewer mutations than adult tumors and within tumors types, most mutations are not shared by the majority of cases.[5,6] Overall, the number of nonsynonymous coding mutations varies from one to 12 per pediatric tumor sample. Outliers exist with higher mutation frequency in a small percent of pediatric tumors that may harbor alterations in DNA repair pathway genes. Despite the relatively low mutation burden, there are many examples where actionable mutations are likely to lead to novel therapeutic interventions in the near future.

There are a handful of pediatric tumors where high-frequency shared genomic alterations are characteristic. Examples include malignant rhabdoid tumors in which *SMARCB1* mutations occur in 100% of cases and may be the sole abnormality, as well as diffuse pontine gliomas where *H3* histone mutations are observed in 78% of cases.[7,8] Such mutations converge on epigenetic pathways, and although these targets are not actionable at the present time, downstream targets in which expression is affected have been identified.

More commonly, recurrent mutations are seen in smaller subsets of samples within a given class of tumors. There was great anticipation that deciphering the genetic landscape of high-risk pediatric tumors, where clinical progress has been stalled, would lead to catalytic advances in treatment. Improving therapy for the most common extracranial solid tumor, neuroblastoma, is a top priority in pediatric oncology. Although the prognosis is favorable for low-stage disease, most patients present with widely metastatic disease. Therapy for stage IV neuroblastoma has improved somewhat, but further progress is urgently needed.[9] In one of the largest sequencing efforts directed at neuroblastoma, 240 cases were examined. Individual samples had on average 14 nonsilent or nonsynonymous mutations.[10] The most commonly seen alterations were *ALK* mutations (9.2%, gain of function), *ATRX* alterations (9.6%, deletions and loss of function mutations), and *PTPN11* mutations (2.9%). Thus, it is somewhat disappointing that neuroblastomas do not contain high-frequency variants suitable for targeted therapy; however, the use of ALK inhibitors for the 10% of patients who carry *ALK*-activating mutations is an important avenue to pursue. This disappointment is tempered by new approaches to inhibit MYCN and its downstream targets. Amplification of the *MYCN* oncogene is observed in 25% of cases but, to date, numerous approaches to target transcription factors like MYC

KEY POINTS

- The genetic landscape of childhood cancer is far less complex than that of tumors that occur in adulthood.
- Tumor profiling has revealed genetic alterations unique to traditional histological tumor subtypes as well as changes that are shared across seemingly disparate tumors.
- With few exceptions, high-frequency shared genetic alterations are not observed, but low frequency individual genetic alterations may coalesce into biological pathways that offer the possibility of novel treatment approaches.
- The impact of precision medicine is best evaluated in the context of carefully controlled clinical trials.

have failed. However, the development of BET bromodomain inhibitors is emerging as a powerful approach to target MYC-overexpressing tumors. These agents effectively displace BRD4, a protein targeted to acetylated lysines, from the *MYCN* promoter, thereby downregulating MYCN expression as well as downstream targets. The clinical efficacy has been documented in preclinical models and clinical trials are underway.[11] Likewise CDK7 inhibitors selectively suppress MYC-driven cancers.[12]

Interestingly, even in tumors that harbor sentinel genetic translocations, there may be surprising heterogeneity of additional genetic alterations. Ewing sarcoma is characterized by translocations between *EWSR1* on chromosome 22 (q11.2) and members of the *ETS* family; usually *FLI1* (11q12). More than 90% of Ewing sarcomas contain *EWSR1* fusions. Recent sequencing efforts have noted that samples had an average of 10 coding variants per tumor, consistent with what has been observed for other childhood cancers.[13,14] However, despite this relatively uniform genetic class, only a minority of sequence variants were shared. The most consistent lesions were *STAG2* mutations, which were observed in only 17% of cases, followed by *CDKN2A* deletions (12%) and *TP53* mutations (7%). *EZH2, BCOR,* and *ZMYM3* mutations were each seen in 2.7% of samples. *STAG2* and *TP53* mutations often coexisted and were associated with an inferior outcome. Thus, the majority of single nucleotide variants were unique. Likewise the poor prognosis alveolar subtype of rhabdomyosarcoma is characterized by genetic fusions between the *PAX3* or *PAX7* genes and *FOXO1*. Interestingly, these tumors have far fewer nonsynonymous mutations compared with fusion-negative embryonal tumors that have a better prognosis (average 6.4 vs. 17.8).[15] Moreover, there was no significant sharing of mutations across *PAX-FOXO1* samples and individual mutations did not converge on biologic pathways (see below).

INDIVIDUAL GENETIC ALTERATIONS MAY CONVERGE ON BIOLOGIC PATHWAYS

Results to date indicate that many samples from patients with a wide variety of histologic subtypes lack high frequency shared genetic alterations. To interpret these results it must be recognized that approximately 50% of the somatic variants detected are likely to be passenger mutations, possibly acquired from the initial nontransformed stem cell of origin.[5] Second, it is likely that although the mutational landscape may vary markedly between tumors of the same histologic or genetic subtype, the lesions may converge on common pathways.

Remarkably, about 50% of embryonal rhabdomyosarcomas contain activating mutations in the RAS pathway (*RAS* [22.4%: *NRAS,* 11.7%; *KRAS,* 6.4%; *HRAS,* 4.3%], *FGFR4* [11.7%], *PI3CA* [7.4%] and *NF1* [5.3%]).[15] Although RAS remains an elusive target there are many downstream inhibitors currently under investigations as well as the U.S. Food and Drug Administration (FDA)-approved MEK1/2 inhibitor trametinib.

Overall survival for the most common pediatric bone tumor osteosarcoma has remained at a plateau for three decades. Osteosarcoma stands out among all pediatric tumors for its relatively high mutation rate and number of structural variations per sample. A recently published analysis showed that on average osteosarcoma samples have 37 nonsynonymous mutations, which is at least three-fold greater than that observed for other pediatric cancers.[16] In addition, osteosarcomas contain frequent copy number alterations including deletions in *RB1, TP53,* and *CDKN2A/B,* and amplifications in *COPS3, CCNE1, CDK4,* and *MYC.* Inactivation of *TP53* either by mutation and/or deletion is seen in three-fourths of cases (some cases have germ line *TP53* mutations), whereas, *RB1* deletion is seen in approximately 60% of samples. Combined *RB1/TP53* inactivation occurs in half of all cases. In examining the mutation spectrum, little to no shared mutations were seen beyond the 22% of samples containing *TP53* mutations. However, gene set enrichment analysis indicates that 24% of patients have tumors with alterations in the PI3K/mTOR pathway. This observation was validated in a genome-wide pooled shRNA screen and murine xenograft experiments confirmed therapeutic efficacy for dual PI3K/mTOR inhibitors (GSK2126458, BEZ235) and the PIK3CA inhibitor (PIK75).

Although the outcome for all subtypes of childhood ALL has improved considerably, patients who relapse have a dismal prognosis even with high-dose chemotherapy and stem cell rescue. In an effort to identify the underlying biologic pathways that drive drug resistance and relapse, many investigators have performed gene expression, copy number, methylation, and sequencing analyses on diagnosis relapse pairs. These efforts have identified alterations enriched at relapse and in some cases these alterations have been shown to alter drug sensitivity to individual agents (e.g., *BTG1* and *TBLXR1* deletions and decreased sensitivity to glucocorticoids and *NT5C2* mutations and resistance to purine analogs).[17,18] However, these alterations occur in a small but significant subpopulation of patients. When changes across three platforms were integrated (copy number alterations, changes in methylation, and gene expression) there was significant convergence on activation of the WNT and MAPK pathways. Activation has been subsequently validated by phosphoflow protein levels and inhibitors of both pathways have been shown to synergize with chemotherapy in cell lines and patient samples.[19-21]

These examples illustrate the value of sequencing a large collection of samples and emphasize the importance of pathway analysis and validation.

PRIMETIME EXAMPLES OF GENETIC PROFILING AND TARGETED THERAPY

The ALK oncogene is perhaps the best example of an emerging new target in pediatric oncology. Almost all (> 90%) pediatric anaplastic large cell lymphomas (ALCL) contain activating ALK fusion transcripts, usually *NPM-ALK.* Inflammatory myofibroblastic tumors (IMT) are quite rare and

most are treated with surgical excision, but 50% of cases also show an *ALK* rearrangement, most commonly with *TPM3* and *TPM4*. Finally, the majority of familial neuroblastomas and, as described above, 8% to 10% of sporadic cases have *ALK* activating point mutations. Another 2% to 3% of sporadic cases have *ALK* amplification. Early phase clinical trial experience with the ALK inhibitor crizotinib (originally designed as an MEK inhibitor) shows a remarkable response in patients with refractory ALCL (eight of nine patients) and IMT (three of seven patients), but less activity in ALK-activated neuroblastoma (one of 11 patients).[22] These encouraging results, in part, led to the development of the currently open Children's Oncology Group (COG) ANHL12P1 randomized phase II trial for newly diagnosed ALCL using brentuximab vedotin or crizotinib in combination with chemotherapy.

Successful introduction of imatinib into conventional chemotherapy for Ph+ ALL has had a profound effect on survival, and this success has been followed by the investigation of the second-generation tyrosine kinase inhibitor, dasatinib in combination with chemotherapy.[1,23-25] Most children can now be successfully cured without the use of stem cell transplantation. Perhaps even more importantly from a population base effect standpoint, approximately 10% of children with standard-risk ALL and 27% of young adults with ALL have "Philadelphia-like" (Ph-like) ALL that share a gene expression profile like Ph+ ALL but lack the BCR-ABL1 fusion protein. These cases often share *IKZF1* deletions, CRLF overexpression, and have a poor prognosis. Recent large-scale sequencing efforts have documented that the overwhelming majority (91%) of samples from patients with Ph-like disease carry kinase-activating alterations.[26] In particular, 12.6% of a recent series of such patients had fusions that would respond to ABL1 inhibitors such as imatinib (e.g., *ABL1*, *ABL2*, *CSF1R,* and *PDGFRB* fusions) and more than one-half had JAK-STAT pathway lesions such as *CRLF2* rearrangements with and without *JAK2* mutations and other JAK-STAT alterations. In vivo and in vitro models have confirmed response to ABL1 inhibitors and JAK1/2 inhibitors, respectively.[26-28] There have now been numerous anecdotal reports of patients with *ABL1* class fusions showing dramatic responses to tyrosine kinase inhibitors.[29,30] As a result, COG plans to open a prospective trial comparing the outcome of patients with ABL1 fusion treated with a combination of dasatinib and chemotherapy with a historic control of recently treated patients (chemotherapy alone).

These two trials for ALK-positive ALCL and Ph-like ALL (as well as the previous two COG studies for Ph+ ALL) illustrate the rapid integration of new agents for newly diagnosed patients in a nonrandomized fashion. Preclinical data indicate that the targets are essential for tumorigenesis and early experience (some anecdotal for Ph-like ALL) shows spectacular clinical efficacy. Given the strong biologic rationale and preclinical data for certain targeted agents a randomized trial may not always be feasible, and in this case the two trials differ remarkably in technical approaches. Simple ALK staining indicates ALK activity, whereas, expression profiling is being used to detect Ph-like ALL followed by a stepwise targeted approach to identify cases appropriate for treatment with tyrosine kinase inhibitors.

TUMOR HETEROGENEITY AND EVOLUTION

In addition to the relative dearth of effective targeted agents, one of the biggest barriers to effective implementation of clinical sequencing in oncology is tumor heterogeneity.[31] Indeed many home grown sequencing efforts have not accounted for this property of cancer populations. In contrast to most adult cancers, pediatric tumors appear to have less genomic instability with the possible exception of osteosarcoma. Thus, endogenous sources of ongoing mutational frequency throughout tumor evolution may be less of an issue in childhood cancer; although, exogenous sources of genome instability through cytotoxic therapy remains a possibility. There is no doubt, however, that multiple subclones exist within a given tumor and subclones may be geographically distinct so that a single biopsy may not capture the full mutational spectrum of a given tumor. In addition, human tumors have been shown to follow a branched chain model in which certain mutations, which are typically acquired early, are truncal drivers, whereas, as others appear to drive subclones (branch drivers). Targeting truncal drivers may provide more clinical benefit. Last, there is evidence to suggest that clones may compete with one another so that targeting one may lead to emergence of the competitor. Conversely, clones may exist in a symbiotic relationship so that targeting one may have a collateral effect on regression of another. All these potential confounding evolutionary features of cancer progression require consideration when designing sequence-based therapeutic interventions.

Acute leukemia provides a convenient model to study tumor evolution considering the feasibility of serial tumor sampling. However, the use of cell-free DNA in the circulation is proving to be a potential option of monitoring solid tumors where access is challenging. As mentioned above, studies have generally showed a complex, nonlinear evolutionary history during which mutations may be acquired independently.[32] Examination of diagnosis and relapse pairs frequently reveals outgrowth of a minor subclone that can be backtracked to diagnosis (Fig. 1). These small subclones may not be detected by conventional NGS approaches. These studies have shown enrichment of genetic alterations (e.g., deletions of *IKZF1*, *MSH6*, *EBF1*, *BTG1,* and *TBL1XR1*, and mutations of *NT5C2* and *RAS* pathway mutations) that account for resistance to conventional chemotherapy.[17-19,33,34] Thus, the outgrowth of these clones is profoundly shaped by the selective forces of the chemotherapy applied. Earlier detection and/or monitoring for emergence of subclones may allow preemptive alteration of conventional agents and/or targeted therapy to prevent overt relapse.

Although targeted therapy has had a profound effect on disease regression for adult tumors like advanced *BRAF*-mutant melanoma and *ALK* fusion non-small cell lung cancer, the beneficial response is short lived with emergence of

FIGURE 1. Clonal Evolution of Relapsed Disease in ALL
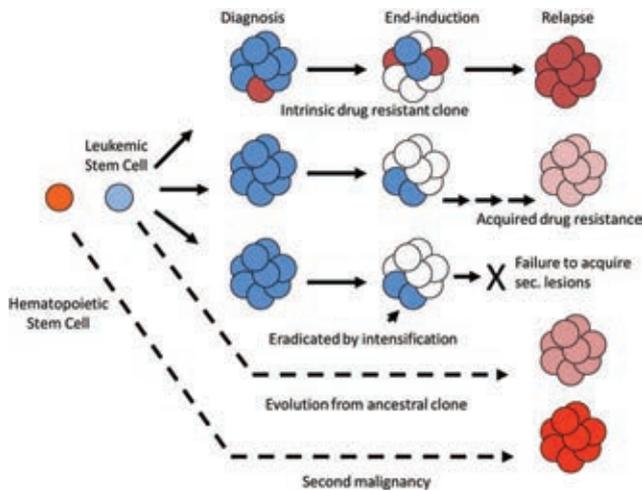
A pre-leukemic stem cell (LSC; light blue) gives rise to frank ALL (dark blue cells). Intrinsically, drug-resistant clones (red) may be present and detected at diagnosis at low levels in approximately 34% of cases. However, relapse might emerge from an ancestral clone or LSC (52% of cases). LSCs and other subclones may survive initial treatment and may acquire additional lesions that result in acquired drug resistance and relapsed disease (52% of cases). Rarely, relapse clones are genetically distinct from that at diagnosis (second malignancy; 6% of cases).[33,45]

resistant subclones either through gatekeeper mutations that interfere with drug-target interaction or off-target resistance through activation of biologic pathways that bypass the mechanism of therapeutic targeting. Based on analysis of samples at relapse, the development of next-generation agents that accommodate gatekeeper mutations and dual pathway inhibitors have shown greater efficacy, yet the enormous repertoire of tumor subclones is likely to be an ongoing issue. In this regard, the nonspecificity of conventional agents may prove to be an advantage when given with targeted agents.

CURRENT CLINICAL EXPERIENCE WITH PEDIATRIC TUMOR SEQUENCING

NGS is now being rapidly incorporated into clinical laboratory settings,[35] which have resulted in the fast growing field of genomic medicine. More often WES is being performed as approximately 85% of disease-causing mutations reside in coding regions of the human genome.[36] This has led to multiple recent studies that reported on the implementation of these tests as well as the evaluation of the clinical utility that exome data can provide in pediatric oncology populations. In a study that examined obtaining informed consent for clinical WES in newly diagnosed solid tumors, 83% of eligible families choose to participate, allowing analysis of both tumor and germ line DNA.[37] No significant differences in enrollment were seen based on race, ethnicity, use of interpreters, or language of consent forms. Additionally, no difference in enrollment was seen based on tumor type or availability of specimens. Of those families that chose to decline, the most commonly stated reason was being overwhelmed by the new diagnosis. Furthermore, of the 83% of

patients that consented to the study, clinically relevant mutations were identified in 28% of tumor cases (22 of 80 cases).[38] Similar data were obtained by another group profiling high-risk and refractory pediatric solid tumors.[39] Using targeted NGS, Sequenom assay or array comparative genomic hybridization individualized cancer therapy recommendations were made in 30% of cases based on profiling results.

In addition to WES, targeted NGS panels are currently being developed that are specifically tailored to capture cancer-related genes and introns of genes commonly rearranged in pediatric tumors. The hybridization capture assay currently offered by Foundation Medicine, which can be completed in 14 to 17 days, surveys 236 genes and 47 introns of genes commonly involved in chromosome translocations. Recent analysis of 400 cases profiled by this method, consisting of both solid and hematopoietic tumors, showed 60% of samples obtained at least one alteration associated with a FDA-approved or experimental therapy in an open clinical trial.[40] Although these studies show that sequencing can lead to therapeutic decisions, additional research is still needed to determine the effect NGS has on overall survival and outcome.

Although most WES studies have focused on somatic variants, germ line data is also routinely profiled in pediatric tumors in tandem to provide an analysis of pathogenic mutations in cancer susceptibility genes as well as mutations present in nononcogenic-related diseases. In a large study surveying 565 genes in 1,120 pediatric cancers, 8.6% of patients were found to have a pathologic or likely pathologic germ line variant.[41] Likewise, 14% of cases harbored a predisposing pathogenic mutation in the germ line DNA in 80 solid tumor cases mentioned previously.[38] This demonstrates that the number of pediatric cancers caused in part by inherited variation may be much higher than anticipated previously, and in many of these cases a family history was not suggestive of a predisposition. Additionally, the discovery of unanticipated incidental germline findings raises a considerable debate about the return of such information to patients.[38] Early recommendations included mandatory return of germ line results on 56 genes associated with 24 inherited conditions, but an early revision of this policy is that patients may opt out from receiving such information.[42]

CLINICAL TRIALS OF PRECISION MEDICINE: PEDIATRIC IMPACT

Given all the challenges discussed, the true effect of precision medicine on patient outcome remains uncertain. It is noteworthy that from 2002 to 2014, 71 agents were approved for use in adult solid tumors, with many qualifying as targeted agents. Although there were striking exceptions, the median improvement in progression-free survival and overall survival was 2.5 months and 2.1 months, respectively.[43] In this context, careful clinical trials that rigorously incorporate NGS would seem to be essential before routine adaptation of this approach at individual centers that treat pediatric oncology patients. Although N-of-1 protocols and molecular tumor boards may add value, the true effect of precision medicine is best measured when bio-

markers and interventions are defined at the outset. The National Cancer Institute (NCI) MATCH prospective clinical trial will open for patients age 18 or older in which standard therapy has failed and who are willing to undergo a rebiopsy.[44] Analysis of approximately 200 genes that have been selected for alignment with a targeted agent will be performed in one of four Clinical Laboratory Improvement Amendment-certified laboratories. The trial will use FDA-approved drugs outside of their indication as well as agents not yet approved but that have shown activity in a given tumor type. The NCI MATCH study will be open to all four adult cooperative groups. NCI is now planning a Pediatric MATCH study with COG, thus, paving the way for precision medicine for all COG members.

SUMMARY AND CONCLUSIONS

Next-generation genomic analysis of pediatric tumors has yielded profound insights into the origins of childhood cancers and has shed light on biologic pathways that drive tumorigenesis and drug resistance. Integration of new agents on a backbone of traditional therapy is being pursued in many tumor types, and there is great anticipation that such approaches will lead to improved outcomes. The integration of NGS into therapeutic decision making for individual patients poses many technical, financial, and biologic challenges. It may be anticipated that such hurdles will be overcome through careful application of precision medicine in the context of rigorous clinical trials.

Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

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PEDIATRIC ONCOLOGY

Translating Survivorship Research into Health Surveillance Guidelines

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Approaches to Reduce the Long-Term Burden of Treatment-Related Complications in Survivors of Childhood Cancer

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OVERVIEW

Advances in diagnostics, treatment strategies, and supportive care have contributed to a marked improvement in outcomes for children with cancer. This has resulted in a growing number of long-term childhood cancer survivors. Currently there are over 360,000 individuals who are survivors of childhood cancer in the United States. However, treatment for patients with childhood cancer with chemotherapy, radiation, and/or hematopoietic stem cell transplantation can result in health-related complications that may not become evident until years after completion of treatment. As a result, several initiatives have been established to help standardize the surveillance for treatment-related late effects in childhood cancer survivors. This review highlights emerging concepts related to commonly reported late effects, such as subsequent malignant neoplasms, cardiovascular disease, and endocrinopathies. It also discusses relevant population-based screening strategies to mitigate the long-term health-related burden in vulnerable populations of survivors.

Advances in diagnostic precision, treatment strategies, and supportive care have resulted in marked improvements in outcomes for children diagnosed with cancer. Overall 5-year survival rates for these children now exceed 80%, resulting in over 360,000 individuals who are survivors of childhood cancer in the United States.[1] Of these, 24% are estimated to have survived more than 30 years since their diagnosis, contributing to the growing number of long-term survivors of childhood cancer in the United States.[1] These survivors are at high risk for developing complications, such as subsequent malignant neoplasms, cardiovascular disease, and endocrinopathies, years after completion of cancer treatment.[2-4] For many of these complications, there are well-established associations between therapeutic exposures and adverse health-related outcomes,[4] which sets the stage for primary prevention (avoidance of certain treatments, when possible) and secondary prevention (screening for and treatment of asymptomatic disease) strategies in these survivors.

Recognizing the need for a systematic plan for surveillance of health-related complications, a number of groups[5-8] have developed risk-based, exposure-related guidelines to facilitate the long-term follow-up care of childhood cancer survivors. These efforts have been further enhanced by an ongoing international effort (International Guideline Harmonization Group [IGHG])[9] to develop uniform recommendations for population-based surveillance. Recommendations for breast cancer[10] and cardiomyopathy[11] screening have been established, and there are a number of ongoing initiatives that will address topics related to reproductive health, other subsequent malignancies, and cardiovascular complications. We present an overview of some of the more commonly reported health-related complications in survivors of childhood cancer and outline current recommendations for early screening and disease prevention.

SUBSEQUENT MALIGNANT NEOPLASMS

Subsequent malignant neoplasms (SMNs), defined as histologically distinct malignancies that develop in children with a primary malignancy, are the leading cause of nonrelapse late mortality.[12-14] The incidence of SMNs in childhood cancer survivors increases with sustained age, with the cumulative incidence exceeding 20% at 30 years after diagnosis of the primary cancer.[13-15] These survivors have an up to sixfold risk of SMNs when compared with age- and sex-matched general population, and the excess risk of SMNs is highest for Hodgkin lymphoma (HL) and Ewing sarcoma survivors (8.7-fold and 8.5-fold, respectively).[15] A recent report[16] found that survivors who develop a first SMN (SN1) are at an especially high risk of multiple occurrences of subsequent neoplasms. Within 20 years from diagnosis of the first SMN, nearly one-half (47%) will develop a subsequent neoplasm. Previous studies have demonstrated that childhood cancer survivors with either a family history of cancer, and even more so, presence of Li-Fraumeni syndrome or hereditary retinoblastoma, carry an increased risk of developing an SMN[17-19]; suggesting that germ line predisposition to cancer may play a role in SMNs.

Commonly reported solid SMNs include breast, thyroid, skin, and brain cancer. There is a well-defined association between radiation exposure that is characterized by a long latency that exceeds 10 years.[13,15] The incidence of many of these solid SMNs continues to increase with longer follow-up, with no plateau of risk over time.[13,15] Other SMNs, such as treatment-associated leukemia (myelodysplastic syndrome/acute myeloid leukemia [tMDS/AML]) are notable for their shorter latency (< 5 years from primary cancer diagnosis), and association with alkylating agent and/or topisomerase-II inhibitor chemotherapy.[20,21] The distinct differences in the onset and role played by specific therapeutic exposures often have resulted in the classification of SMNs into two distinct categories: (1) radiation-related solid SMNs, and (2) chemotherapy-related tMDS/AML.[21]

Radiation-Associated Solid Subsequent Malignant Neoplasms

Breast cancer. Female childhood cancer survivors treated previously with radiation involving the chest area (e.g., mantle, mediastinal, whole lung, and axillary fields) are at high risk of developing breast cancer later in life.[22-24] In this population, the cumulative incidence of breast cancer ranges from 12% to 20% by age 45,[22-24] an incidence equivalent to that seen in women who have a *BRCA* gene mutation (incidence 10% to 19% at age 40).[24] In childhood cancer survivors, the latency of breast cancer after chest radiation ranges from 8 to 10 years, and the risk increases in a linear fashion with radiation dose.[24,25] The relative risk is 6.4 at a dose of 20 Gy and it increases to 11.8 at a dose of 40 Gy.[24,25] Breast cancer risk is attenuated among women who also received radiation to the ovaries, which reflects the role of hormone stimulation on patients with radiation-induced breast cancer.[24,25]

Screening recommendations[10] for women exposed to 20 Gy or more of radiation to the chest area (Table 1) include monthly breast self-examination beginning at puberty, annual clinical breast examination beginning at puberty until

KEY POINTS

- There are a growing number of long-term survivors of childhood cancer at risk for treatment-related complications later in life.
- There are well-established associations between therapeutic exposures and adverse health-related outcomes such as subsequent malignant neoplasms, cardiovascular disease, and endocrinopathies.
- A number of risk-based exposure-related guidelines have been established to facilitate the long-term follow-up care of childhood cancer survivors.
- These surveillance guidelines are an integral component of the lifelong follow-up of childhood cancer survivors.
- Studies are needed to evaluate the efficacy of these recommendations in survivors who have the highest risk for treatment-related complications.

age 25, and clinical breast examination every 6 months with annual mammograms and MRIs beginning 8 years after radiation exposure or at 25 years (whichever occurs last).

Thyroid cancer. Survivors at risk include those treated with head, neck, chest, mantle, craniospinal, or total-body irradiation (TBI).[26,27] The association between radiation dose and thyroid cancer is curvilinear, with risk increasing at low to moderate doses and decreasing at doses more than 30 Gy because of cell-killing effect.[27-29] Additional risk factors for developing thyroid cancer include younger age at diagnosis, female sex, and longer duration of follow-up.[27,29,30]

Childhood cancer survivors treated with radiation affecting the thyroid should have lifelong annual screening exams for thyroid abnormalities (Table 1). Although some have advocated the use of thyroid ultrasonography to screen for thyroid cancer in previously irradiated patients,[31,32] the Children's Oncology Group (COG) currently recommends careful palpation annually.[5] The indolent course and excellent outcome of the vast majority of second primary thyroid cancers has prompted debate about the risks versus the benefits of ultrasound screening in at-risk survivors.[32,33]

Brain tumor. Childhood cancer survivors have an 8.1 to 52.3 times higher incidence of developing subsequent brain tumors compared to the general population.[34] High-grade gliomas and meningiomas are the two most common SMNs, and the vast majority of these tumors develop in children treated with cranial radiation.[34,35] Although the risk for subsequent brain tumors demonstrates a linear relation with radiation dose, the dose-response appears to be weaker for gliomas than for meningiomas.[15,34]

Survivors treated with cranial radiation should have an annual follow-up that includes a targeted history and a comprehensive neurologic examination.[5] The additional benefit of screening using neuroimaging (e.g., MRI) is not known, but it remains an active area of investigation.[35,36]

Skin cancer. Nonmelanoma skin cancer (NMSC; e.g., basal cell, squamous cell) is one of the most frequent SMNs in childhood cancer survivors.[15,37] Compared to the general population, childhood cancer survivors have a fivefold increased risk of NMSC, and 90% of tumors occur within the radiation field.[37] Although melanomas are less common than NMSCs, survivors of hereditary retinoblastoma are at an especially high risk.[38,39] This may be the result of common etiologic factors between the two tumor types.

Areas of the skin previously exposed to radiation should be monitored closely during annual physical examinations, with prompt referral to dermatology for evaluation of nevi that are concerning for skin cancer.[5]

Colorectal cancer. Recent reports[13,40,41] from aging cohorts of childhood cancer survivors have highlighted the markedly increased risk of digestive SMNs (absolute excess risk in survivors older than 40, 5.9 per 100,000), with the highest risk

TABLE 1. Risk-Based Screening for Subsequent Malignant Neoplasms

Potential Late Effect	Cancer Treatment	Screening Tests
Breast Cancer	Radiation to the chest area	Females: Clinical breast exam yearly beginning at puberty until age 25, then every 6 mo Mammogram and breast MRI yearly for patients who received ≥ 20 Gy beginning 8 yr after radiation or at age 25, whichever occurs last. For patients who received 10-19 Gy, clinicians should discuss benefits and risks/harms of screening with patients.
Thyroid Cancer	Radiation to the thyroid	Yearly physical examination
Brain Tumor	Cranial irradiation	Yearly targeted history and comprehensive neurologic examination
Skin Cancer	Radiation to the skin	Yearly physical examination
Colorectal Cancer	Abdominal/pelvic irradiation	Colonoscopy every 5 yr (minimum for patients who received ≥ 30 Gy, beginning 10 yr after radiation or at age 35, whichever occurs last)
	Spinal irradiation	
tMDS/AML	Alkylating agents, topoisomerase-II inhibitors	Yearly targeted history/physical examination

Abbreviations: mo, months; yr, years; tMDS, trilineage myelodysplasia; AML, acute myeloid leukemia.

seen in survivors exposed to abdominal radiation. In fact, by age 50, the incidence of colorectal cancer (CRC) for survivors treated with direct abdominopelvic radiation is comparable to the risk in individuals with at least two first-degree relatives affected by CRC.[13]

For survivors treated with 30 Gy or more of abdominopelvic radiation, the COG recommends a screening colonoscopy every 5 years, beginning 10 years after radiation or at age 35, whichever occurs last.[5]

Chemotherapy-Related TMDS/AML

Survivors treated with alkylating agents (e.g., cyclophosphamide, ifosfamide, mechlorethamine, melphalan, busulfan, nitrosureas, chlorambucil, dacarbizine, and platinum compounds) or topoisomerase-II inhibitors (e.g., epidophyllotoxins, anthracyclines) are at risk for developing tMDS/AML.[18,42] The risk of alkylating-agent–associated tMDS/AML is dose-dependent, with a latency of 3 to 5 years after exposure. Typically, it is associated with cytogenetic abnormalities involving chromosomes 5 (−5/del[5q]) and 7 (−7/del[7q]). Topoisomerase-II inhibitor-related tMDS/AML has a shorter latency (< 3 years), and is associated with balanced translocations involving chromosome bands 11q23 or 21q22.[18,42]

Since chemotherapy-related tMDS/AML usually develops by 10 years after exposure to these agents, current recommendations are to monitor at-risk survivors with a targeted history and physical examination for up to 10 years postexposure.[5] A complete blood count and bone marrow examination may be warranted for those with a history or physical examination findings suspicious for tMDS/AML (e.g., easy bruising, fatigue, pallor, and petechiae).[5]

CARDIOVASCULAR DISEASE

Cardiovascular disease is a major health problem in children and adults after treatment for childhood cancer.[43] In fact, childhood cancer survivors have a sevenfold increased risk of cardiac death when compared with the general population.

The risk is highest in survivors of HL, kidney tumors, and Ewing sarcoma.[12,14] Cardiovascular complications after treatment for childhood cancer include cardiomyopathy/heart failure, coronary artery disease, valvular disease, conduction abnormalities, and pericardial disease.[43] Outcome following onset of cardiovascular complications such as heart failure is especially poor, with 5-year survival less than 50%.[44]

In survivors of childhood cancer, there is a long latency between cancer treatment and onset of clinically overt cardiovascular disease.[43] As a result, there have been a number of initiatives to facilitate early detection and treatment of asymptomatic disease,[5,7,8,42] setting the stage to minimize the long-term burden as a result of these complications. Recently, an international collaborative effort was organized to develop evidence-based guidelines for cardiomyopathy surveillance in at-risk survivors of childhood cancer.[11] Additional surveillance guidelines pertaining to coronary artery disease, valvular disease, conduction abnormalities, and pericardial disease are pending. When completed, these recommendations may facilitate the implementation of uniform evidence-based guidelines to minimize the long-term burden as a result of cardiovascular disease in these survivors.

Cardiomyopathy

Childhood cancer survivors treated with cardiotoxic therapies (anthracycline chemotherapy and/or chest radiation) are at risk for developing asymptomatic cardiomyopathy that can progress to symptomatic heart failure over time.[43] The risk of heart failure is 15-fold greater in survivors of childhood cancer when compared to the general population,[3] and there is a dose-dependent association with anthracycline (doxorubicin, daunorubicin, epirubicin, idarubicin, and mitoxantrone) chemotherapy and risk of heart failure. This risk is further increased by exposure to chest radiation.[43] Among anthracycline-exposed survivors, asymptomatic cardiomyopathy is characterized by a decrease in left ventricular systolic function, which often presents with a clinical picture similar to dilated cardiomyopathy.[43] Patients treated with

chest radiation may have a combination of dilated and restrictive cardiomyopathy.[43]

Who Needs Surveillance?

It is well established that children and adolescents treated with anthracyclines and/or chest radiation are at increased risk of developing cardiomyopathy when compared to the general population. In fact, there appears to be an exponential increase in risk of cardiomyopathy with increased lifetime cumulative anthracycline dose. The highest risk is among survivors treated with 250 mg/m^2 or more.[46-48] Although it is generally believed that the risk for cardiomyopathy among those treated with less than 100 mg/m^2 is very low, there appears to be no clear cutoff for a safe anthracycline dose.[46-48] Patients treated with 35 Gy or more of chest radiation also are at high risk of developing cardiomyopathy, and there remains an elevated risk among those treated with lower doses (15 Gy to < 35 Gy) of radiation.[46,47] However, no data exist to suggest that children treated with lower doses (e.g., < 15 Gy in < 2 Gy daily fractions), such as TBI alone, are at increased risk of cardiomyopathy.

Survivors treated with anthracyclines and/or radiation therapy involving the heart region should be aware of the risk of cardiomyopathy.[11] Furthermore, the IGHG cardiomyopathy surveillance guidelines strongly recommend screening for survivors who have a fourfold or greater risk (anthracycline dose ≥ 250 mg/m^2, or chest radiation dose ≥ 35 Gy, or both anthracycline and radiation exposure) of heart failure when compared to those not treated with anthracyclines and/or chest radiation.[11] Screening may be considered for survivors who have a lower (1.5-fold) but increased risk of heart failure (anthracycline dose < 250 mg/m^2, or chest radiation dose 15 to < 35 Gy).[11]

What Is Optimal Surveillance Modality?

Echocardiographic measurements such as shortening fraction or ejection fraction are the most frequently used tests in childhood cancer survivors to assess the left ventricular function of the heart.[43] An increasing number of studies also are evaluating the role of other echocardiographic parameters, such as wall stress, diastolic function, and isovolumetric relaxation time in routine surveillance.[43,49,50] Currently, studies evaluating the predictive value of these parameters for the development of heart failure or mortality in survivors are lacking. Other, nonechocardiographic imaging approaches to screening that have been evaluated include radionuclide angiography and cardiac MRI (CMR).[43,51] However, radiation exposure from radionuclear tests and the high costs of CMR limit the applicability of these tests for population-based screening. Finally, cardiac biomarkers (NT-Pro-BNP, BNP ANP) play an important role in screening for heart failure in the nononcology population.[43] However, at this time, the diagnostic value of these markers to detect asymptomatic cardiomyopathy in childhood cancer survivors appears to be suboptimal.[11]

No randomized clinical trials have studied the effect of screening of childhood cancer survivors by echocardiography on later outcomes, such as heart failure or cardiac mortality. However, decision-modeling studies[52,53] have found that echocardiographic screening in survivors of childhood cancer can be cost-effective when compared to no screening, which supports the screening recommendations outlined below.

Echocardiography should be used as the primary cardiomyopathy surveillance modality for assessment of left ventricular systolic function in survivors treated with anthracyclines or chest radiation.[11] Screening with radionuclide angiography or CMR may be considered in patients for whom echocardiography is not technically feasible or optimal. Additional diagnostic studies, such as cardiac blood biomarkers, should be considered in conjunction with imaging, based on availability of resources and clinical suspicion for cardiac dysfunction.[11]

At What Frequency and for How Long Should Surveillance Be Performed?

No data are available on the rate of cardiac function deterioration in childhood cancer survivors. Moreover, a paucity of studies describes the incidence of heart failure more than 30 years after cancer diagnosis. Recognizing these limitations, current recommendations on initiation, frequency, and duration of screening are largely based on consensus.

Routine surveillance is recommended for survivors at high risk (anthracycline dose ≥ 250 mg/m^2, or chest radiation dose ≥ 35 Gy, or both anthracycline and radiation exposure) for cardiomyopathy, to begin no later than 2 years after completion of cardiotoxic treatments and repeated at 5 years after diagnosis and continued every 5 years thereafter. More frequent screening may be reasonable in these survivors.[11] Specific screening recommendations for low- to moderate-risk patients should take into consideration the relative risk of heart failure in these populations, along with cost and benefits associated with lifelong screening.[11]

What Should Be Done When Abnormalities Are Identified?

Primary care providers or oncologists who treat childhood cancer survivors should work closely with their cardiology colleagues to ensure that timely and age-appropriate follow-up is provided to all at-risk survivors. To date, no randomized studies have evaluated the efficacy of interventions in survivors of childhood cancer with asymptomatic cardiomyopathy on heart failure risk reduction. However, well-established general pediatric[54] and adult-onset[55] heart failure treatment guidelines may facilitate the implementation of early interventions to minimize long-term morbidity in these survivors.

Cardiology consultation is recommended for patients who have abnormal cardiac function that is detected during surveillance. When possible, pharmacologic intervention following diagnosis of cardiomyopathy should be personalized and should take into consideration existing age-appropriate treatment guidelines.[11]

Additional Considerations

Studies conducted of nononcology populations support the benefits of interventions to reduce modifiable risk factors, such as obesity, smoking, hypertension, diabetes, and dyslipidemia.[56,57] Childhood cancer survivors are at a higher risk of developing many of these conditions when compared to the general population, which places them at increased risk of developing cardiovascular disease.[58,59] In fact, survivors with hypertension or diabetes in addition to past exposure to anthracyclines and/or radiation are at an especially high risk of developing cardiomyopathy and heart failure.[60] Findings from studies of nononcology populations strongly suggest that routine screening for these risk factors can be beneficial and set the stage for interventions (e.g., lifestyle modification and pharmacologic therapy) to mitigate adverse cardiovascular outcomes. Lastly, cardioprotectants such as dexrazoxane have been shown to minimize cardiac injury shortly after anthracycline administration without compromising its anti-tumor efficacy.[61,62] However, long-term data on efficacy of dexrazoxane is lacking. Studies are needed to address this gap in knowledge, setting the stage for the implementation of primary prevention strategies in survivors at highest risk for developing cardiovascular disease.

ENDOCRINE COMPLICATIONS
Thyroid Disorders

Primary hypothyroidism. Primary hypothyroidism frequently occurs after treatment for patients with childhood cancer. Survivors at risk include those treated with radiation to the thyroid gland, including nasopharyngeal, cervical, mantle/supraclavicular, and craniospinal fields, as well as those exposed to TBI.[63-67] The risk of primary hypothyroidism is observed beginning at about 10 Gy of thyroidal irradiation and it increases as the dose of radiation increases above this dose.[63] The risk is greatest within the first 5 years after radiation, but it continues to increase over time. Other risk factors include female sex, white race, and older age at diagnosis.[63]

Patients treated with radiolabeled agents, such as 131-I-metaiodobenzylguanidine[68,69] or 131-I-labeled monoclonal antibody,[70,71] and those treated with tyrosine kinase inhibitors,[73] also are at risk. Although standard-dose chemotherapy alone does not appear to be a risk factor for hypothyroidism,[63] patients who have received stem cell transplants following treatment with myeloablative doses of alkylating agents (e.g., busulfan and cyclophosphamide) are at increased risk for developing primary hypothyroidism.[73]

At-risk childhood cancer survivors should have their thyroid function serially monitored, generally at least annually. Measurement of plasma levels of thyroid-stimulating hormone (TSH) is the most sensitive means of diagnosing primary hypothyroidism (Table 2). Since hypothyroidism can develop more than 25 years after cancer treatment, the need for lifelong screening is essential.[74]

Hyperthyroidism. Treatment-related hyperthyroidism occurs less often than primary hypothyroidism in childhood cancer survivors. It most often results after exposure of the thyroid gland to radiation. In survivors of HL, a radiation dose of more than 35 Gy to the thyroid has been identified as a risk factor for developing hyperthyroidism.[63] Survivors of acute lymphoblastic leukemia treated with a radiation dose of more than 15 Gy to the thyroid also appear to have an increased risk of hyperthyroidism.[64] Immune-mediated hyperthyroidism, as a result of adoptive transfer of abnormal clones of T or B cells from donor to recipient, also has been reported after stem cell transplantation.[73]

Given the low incidence of hyperthyroidism, routine screening is not currently recommended. However, at-risk survivors who present with clinical signs or symptoms (e.g., unexplained weight loss, tachycardia, bilateral exophthalmos, or goiter) suggestive of hyperthyroidism should have, at minimum, a blood level of TSH. A TSH level below the lower limit of normal is highly suggestive of a diagnosis of hyperthyroidism and warrants referral to an endocrinologist for further work up.

Gonadal Dysfunction: Men

The human testis has two primary functions: sperm production and testosterone production. One or both of these functions may be negatively affected by cancer treatment. Germ cells and Sertoli cells form the seminiferous tubules in which spermatogenesis occurs; Leydig cells are responsible for the production of testosterone.

Germ cell dysfunction. Exposure of the sperm-producing cells to radiation and/or certain types of chemotherapy may result in oligo/azoospermia.[75] Chemotherapeutic agents commonly associated with impaired spermatogenesis include mechlorethamine, cyclophosphamide, ifosfamide, procarbazine, busulfan, and melphalan, which are all alkylating agents.[76,77] Risk is dose-dependent, but individual responses vary greatly.[77] Although earlier studies suggested that younger age at treatment was associated with a lower risk of germ cell dysfunction, the data are inconclusive.[76,77]

The testicular germinal epithelium is exquisitely sensitive to radiation. Sperm production may be impaired at radiation doses as low as 0.15 Gy with permanent sterility common following testicular doses of more than 6 Gy.[76] Impaired sperm production may result from direct testicular radiation or scatter from adjacent treatment fields, such as the pelvis, bladder, or inguinal/femoral area. Germ cell dysfunction is present in virtually all men treated with TBI.[73]

Although a variety of clinical (e.g., decreased testicular volume) and biochemic markers (e.g., raised plasma concentrations of follicle-stimulating hormone (FSH) and reduced plasma concentrations of inhibin-B) have been associated with impaired sperm production in population studies. None, however, is suitable as a surrogate test for a given patient's ability to produce sperm because of poor sensitivity and/or specificity.[78] Thus, currently, a sperm analysis in a sexually mature patient is the only definitive test available to determine a survivor's ability to produce sperm.

TABLE 2. Risk-Based Screening for Potential Endocrinopathies Following Cancer Treatment

Potential Late Effect	Cancer Treatment	Screening Tests
Thyroid Dysfunction	· Radiation impacting the thyroid · Agents labelled with 131-I · Tyrosine kinase inhibitors	· TSH, Free T4
Gonadal Dysfunction (Female)	· Alkylating agents · Nitrosoureas · Cisplatin · Radiation to the gonads	· Physical exam with Tanner staging · LH · FSH
Gonadal Dysfunction (Male)	· Alkylating agents · Nitrosoureas · Cisplatin · Radiation to the gonads	· Physical exam with Tanner staging · LH · FSH · Testosterone

Abbreviations: LH, luteinizing hormone; FSH, follicle stimulating hormone; TSH, thyroid stimulating hormone.

Leydig cell dysfunction. Leydig cells are susceptible to radiation-induced damage at higher doses than those associated with germ cell dysfunction. Risk is directly related to testicular radiation dose and inversely related to age at treatment.[79] Although the majority of men who receive less than 20 Gy fractionated radiation to the testes will produce normal amounts of testosterone, most prepubertal males who receive radiation doses of 24 Gy or greater to the testis will develop Leydig cell failure.[80] Chemotherapy alone rarely results in Leydig cell failure, although subclinical Leydig cell dysfunction has been reported following treatment with alkylating agents.[79]

Leydig cell failure will result in pubertal delay or arrest, if it occurs before or during puberty, and in reduced libido, erectile dysfunction, decreased bone mineral density, and decreased muscle mass if it occurs after completion of normal puberty. Patients who are noted to have developed any of the above symptoms after gonadotoxic therapy should be assessed for Leydig cell failure.

Men treated with 20 Gy or more radiation to areas that may affect the testes (flank/hemiabdomen, whole abdomen, inverted Y, pelvic, prostate, bladder, iliac, inguinal, femoral, testicular, total lymphoid, or TBI) should have periodic screening with LH and an early-morning testosterone level beginning at the time of puberty (e.g., by age 14; Table 2).[5] Elevated serum levels of LH with low levels of testosterone are consistent with a diagnosis of Leydig cell failure.

Gonadal Dysfunction: Women

Because of the interdependence of sex steroid-producing cells and oocytes within the ovarian follicle, ovarian failure results in impairment of both sex hormone production and fertility.

Ovarian dysfunction may result from treatment with gonadotoxic chemotherapy, radiation affecting the ovaries, or surgical removal of the ovaries.[81] Chemotherapy-induced ovarian failure typically results from treatment with high-dose alkylators,[82,83] particularly when administered in prep-

aration for stem cell transplantation.[84] Risk is directly correlated with cumulative dose and older age at exposure.

Women treated with radiation affecting the ovaries (spinal, flank, hemiabdomen below the iliac crest, whole abdomen, inverted Y, pelvis, vagina, bladder, iliac lymph nodes, total lymphoid system, or total body) are at increased risk for ovarian failure.[81-83] Doses to the ovary exceeding 10 Gy are associated with a very high risk of ovarian failure.[82] When ovarian transposition is performed before radiotherapy, however, many younger women retain ovarian function.[79] Irradiation at an older age confers a greater risk of ovarian failure.

Women who have normal ovarian function at the end of treatment with potentially gonadotoxic therapy remain at risk for premature menopause later in life and should be counseled accordingly.[82]

Although female survivors treated with high-dose alkylators and/or pelvic irradiation have been shown to be less likely to experience a pregnancy when compared with sibling comparators,[85,86] those who do achieve pregnancy after treatment with chemotherapy alone do not appear to have adverse pregnancy outcomes.[87] Survivors treated with pelvic irradiation, who become pregnant, however, are at a higher risk of stillbirth and neonatal death and having offspring who are premature, have low birth weight, and are small for gestational age.[85,88]

Among survivors of childhood cancer who achieve a successful pregnancy, their offspring do not appear to be at increased risk of congenital anomalies or genetic defects.[85,89,90]

If ovarian failure occurs before pubertal onset, delayed puberty and primary amenorrhea will result. In those in whom ovarian function is lost during or after puberty, pubertal arrest, secondary amenorrhea, and symptoms of menopause will occur. If these symptoms are noted along with elevated gonadotropins, a referral should be made to an endocrinologist or gynecologist for consideration of hormone replacement therapy.

All women treated with the gonadotoxic therapies mentioned above should have periodic screening with LH and FSH levels, as well as careful Tanner staging, to monitor pubertal progression (Table 2). Elevated gonadotropin levels are consistent with primary ovarian dysfunction. Although plasma levels of anti-mullerian hormone (AMH) have been shown to correlate with ovarian reserve in adult women, there are no long-term data correlating AMH levels in children and adolescents and subsequent ovarian function and fertility.[91] Therefore, measurement of AMH levels is not currently recommended in the clinical management of survivors under age 25.

CONCLUSION

Research on survivorship-related issues has identified important associations between certain therapeutic exposures and long-term complications in survivors of childhood cancer. This has facilitated the development of a number of recommendations for early screening in asymptomatic sur-

vivors. Ongoing studies exploring gene-environment interactions[92] continue to refine our understanding of high-risk categories. Studies are needed to integrate emerging information on genetic susceptibility with established clinical risk factors. Novel interventions aimed at reducing the long-term burden in survivors at highest risk for treatment-related late effects also are needed. Multidisciplinary collaboration between primary care providers, oncologists, and other medical specialists is integral to the successful implementation of these interventions.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked "L" indicate leadership positions. Relationships marked "I" are those held by an immediate family member; those marked "B" are held by the author and an immediate family member. Institutional relationships are marked "Inst." Relationships marked "U" are uncompensated.

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PROFESSIONAL DEVELOPMENT

The Challenge to Stay Current: Incorporating Technology into Practice

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Advances in Website Information Resources to Aid in Clinical Practice

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OVERVIEW

The World Wide Web, which has been widely implemented for roughly two decades, is humankind's most impressive effort to aggregate and organize knowledge to date. The medical community was slower to embrace the Internet than others, but the majority of clinicians now use it as part of their everyday practice. For the practicing oncologist, there is a daunting quantity of information to master. For example, a new article relating to cancer is added to the MEDLINE database approximately every 3 minutes. Fortunately, Internet resources can help organize the deluge of information into useful knowledge. This manuscript provides an overview of resources related to general medicine, oncology, and social media that will be of practical use to the practicing oncologist. It is clear from the vast size of the Internet that we are all life-long learners, and the challenge is to acquire "just-in-time" information so that we can provide the best possible care to our patients. The resources that we have presented in this article should help the practicing oncologist continue along the path of transforming information to knowledge to wisdom.

The World Wide Web, proposed by Tim Berners-Lee and Robert Cailliau on November 12, 1990, and widely implemented since 1994, is humankind's most impressive effort to aggregate and organize knowledge to date (Fig. 1).[1] Although the total number of Internet sites is constantly changing, a recent survey estimated that there are 876,812,666 sites with a total information content of 5-million terabytes of data.[2] The medical community was slower to embrace the Internet than others but has now caught up. The current generation of medical students may not recall a world before the Web, mobile telephony, and cheap computing power.[3] As an example of the Web's pervasiveness, a 2009 study found that a majority of junior physicians were using Google (80%) or Wikipedia (70%) in their daily clinical practice.[4]

BACKGROUND: THE ORGANIZATION OF KNOWLEDGE

At its core, the Internet operates by organizing knowledge, both intentionally and informally. There are many useful paradigms for understanding knowledge organization (e.g., explicit versus tacit; individual versus organizational; novel versus learned). The Internet could be framed in any of these dimensions, but for our purposes the data, information, knowledge, wisdom (DIKW) framework, which was introduced in a rudimentary form as early as 1955, offers a very useful starting point.[5,6] This schema is usually represented by a pyramid, where the foundation is raw *data*. For the Inter-

net, this might be an Internet Protocol (IP) address (e.g., 23.21.100.117) or the American Standard Code for Information Interchange codes representing individual characters on a webpage. The next level in the pyramid is *information*, which introduces basic meaning to data, such as "what," "where," and "how much." For example, the IP address 23.21.100.117 points to the uniform resource locator (URL) www.cancer.net. *Knowledge* is the introduction of context and content to information. This is sometimes referred to as "know-how" and is the core goal of many Internet-based resources, which are often referred to as *knowledge bases* (this term is formally used to refer to a machine-readable knowledge resource but in practical terms is used more broadly). Finally, *wisdom* is the most difficult part of this schema to describe, as there is some disagreement on what exactly wisdom represents and whether it can only be manifest as a human endeavor, as opposed to a collective experience such as the Internet.[7]

For the practicing oncologist, the Internet resources most useful in day-to-day practice will have some overlap across the DIKW framework but will be primarily in the knowledge sphere. As described below, the sheer volume of information related to cancer is impossible to master, yet most practitioners desire to have the final say in their practice of medicine (i.e., the application of wisdom to knowledge). We now turn to an overview of some of the current resources available to the practicing oncologist, in three parts: (1) general medical knowledge bases; (2) oncology-specific resources; (3) social

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FIGURE 1. The Internet "Universe" as of the End of 2011, Showing the Top 350,000 Websites Representing 196 Countries
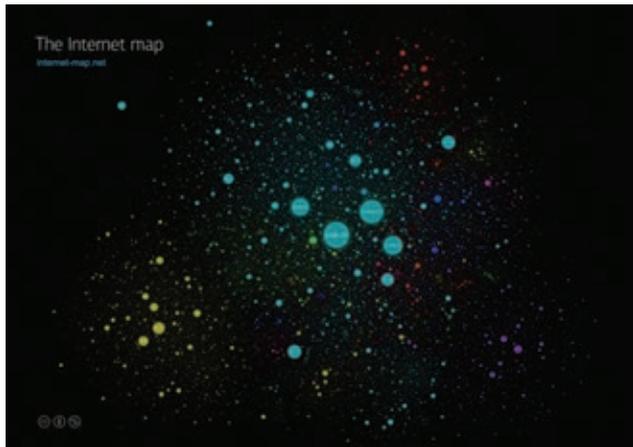
Every website is a circle on the map, and its size is determined by website traffic—the larger the amount of traffic, the bigger the circle (Google.com is the largest). Color is based on the country where the website is hosted (teal being the United States). Users switching between websites form links, and the stronger the link, the closer the websites tend to arrange themselves to each other.
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media outlets of interest to the medical practitioner. Although we have attempted to be exhaustive in this overview, we apologize in advance for any unintentional oversights or omissions.

GENERAL MEDICAL KNOWLEDGE BASES

Online medical compendia and knowledge bases are among the most popular resources for clinical queries. Although not specific to oncology, resources such as UpToDate, Ovid, PubMed, Google, Medscape, and Wikipedia contain information pertaining to many topics relevant to practicing on-

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KEY POINTS

- The Internet is vast and is now used on a regular basis by the majority of physicians, especially those that were born into the "digital generation."
- The organization of the Internet can be understood by applying the data, information, knowledge, wisdom management framework.
- General medical knowledge bases (e.g., PubMed, UpToDate, and Wikipedia) each have advantages and disadvantages for the practicing oncologist.
- There are an increasing number of oncology-specific website resources, including those maintained by professional organizations such as the American Society of Clinical Oncology and unaffiliated entities.
- Social media will take a role of increasing importance for the practicing oncologist, although it must be approached with caution, especially given the for-profit nature of many of the current endeavors.

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cologists. Each resource uses different models to create, organize, aggregate, and present information. Google and Wikipedia are free for use (although Google is supported by advertisements); Medscape is free but requires an account for access; and Ovid and UpToDate require paid subscriptions. With the vastness of oncology literature and the diversity of potential information needs, no one information resource or search strategy is consistently superior.[8] Resources with higher-level reviews (knowledge and wisdom in the DIKW paradigm) will lack the depth and immediacy of primary literature; literature searches (data and information) are more time consuming as the reader must sift through irrelevant results. A savvy information consumer will be familiar with the advantages of multiple knowledge bases. We describe some of the more well-known resources in detail.

PubMed

Developed and maintained by the National Center for Biotechnology Information, PubMed is a free online search engine of the MEDLINE database containing over 24-million citations of biomedical and health literature.[9] The primary user interface consists of a single search field, but multiple advanced search options are possible using specific filters and syntax. Given the vast size of the MEDLINE database (Fig. 2), searches to produce only relevant articles are difficult. Using multiple search terms, Booleans, and additional search tools will produce more relevant results.[10] Some training programs, such as the University of California, San Francisco's Program in Medical Education for the Urban Underserved,[11] explicitly teach searching strategies. For most currently practicing clinicians, optimizing the use of PubMed is an example of "on-the-job training." PubMed indexes large amounts of biomedical literature in near real time; therefore, it is likely to outperform other information resources when searching for recently published information, primary literature, or uncommon questions. However, for general questions other information resources could be considered.

Google

The most popular search engine in the world, Google (Google Inc. Mountain View, CA), is a common starting point for medical queries. The algorithm by which Google produces search results, PageRank, performs numerical weighting to websites based on the number and authoritativeness of webpages that link to them.[12] This produces search results based on relevancy to the entire population of Internet users. Google Scholar (scholar.google.com) restricts searches to scientific literature, such as conference proceedings (which are not generally indexed in MEDLINE). Since a physician-specific version of Google does not exist, using generic terms would be more likely to return websites without information directed specifically at clinicians.[13] A savvy "googler" would use technical terminology for search terms that would be specific to sources directed at clinicians.

FIGURE 2. Growth of "Cancer" References Indexed in MEDLINE
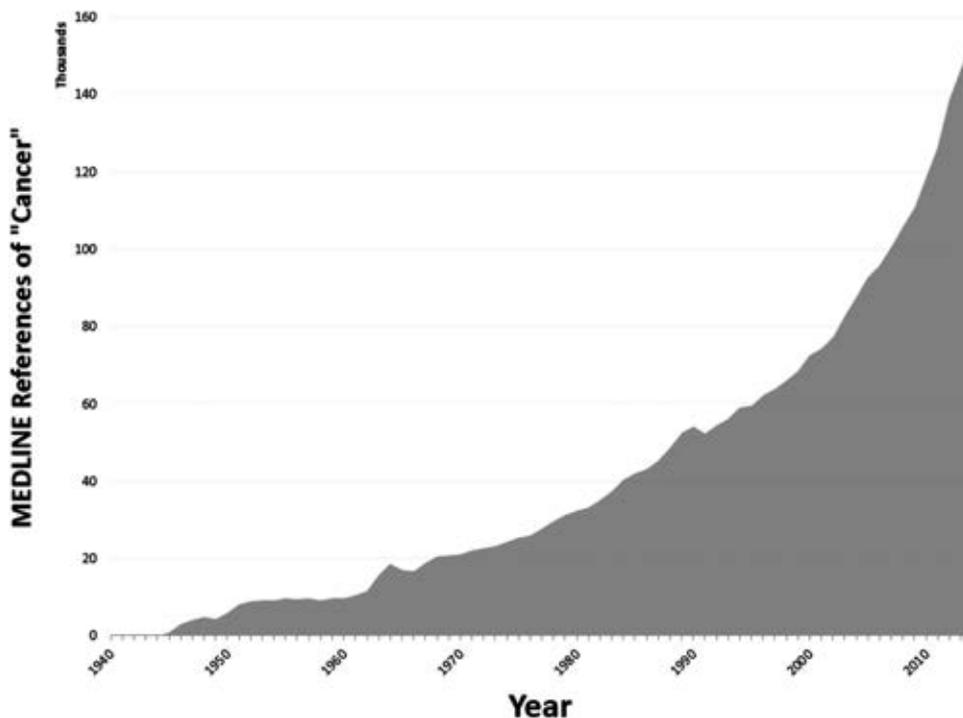
In 2014, 154,654 articles referencing cancer were added to MEDLINE. This amounts to a new article approximately every 3 minutes for the entire year. Extracting utility from this deluge of information for a clinician is impossible without the help of digital searches and information aggregators. Depending on the resource used and the information sought, different strategies must be employed to efficiently find accurate information.

UptoDate

The subscription service UpToDate (Wolters Kluwer NV, Alphen aan den Rijn, the Netherlands) provides original content rather than aggregation of existing resources. The oncology content is provided via two editors in chief, three deputy editors, 35 section editors, and approximately 1,100 authors.[14] Article content draws from primary articles, national guidelines, text books, and expert opinion to generate knowledge and wisdom. Insomuch as there is variation in clinical practice; articles can also represent these regional, institutional, or personal variations. Although articles are updated continuously, the human authors do not necessarily update content immediately on newly published evidence. The trade-off for this content curation is a filtering of irrelevant information that encumbers searches of the primary literature, such that searching content in UpToDate results in satisfactory answers faster than a search engine such as PubMed.[15,16] For clinicians who have access to UpToDate, it can serve as an efficient means of reviewing clinical content but would require additional searching to find "breaking news" information or primary literature.

Ovid

Another Wolters Kluwer subscription service, Ovid is a content aggregator that provides searches across 307 books, 74 journals, 12 databases, and nine collections of oncology content predominantly published by Wolters Kluwer.[17] Additionally, OvidMD is a curated resource for clinician queries optimized to return clinically relevant results. The OvidMD platform also links to UpToDate content for individuals with accounts on both platforms. As such OvidMD operates as something of a hybrid between a content aggregator as well as a curated source of primary content.

Medscape

Similar to Ovid, Medscape (WebMD, New York City, NY) is a hybrid of content aggregator with authors of reviews and literature synopses; however, in contrast it is free to use but requires a login. Additionally, Medscape and its parent company, WebMD, exist in a content zone targeting somewhere between medical professional and lay audience. Medscape has not been evaluated against other information resources in the published literature.

Wikipedia

Wikipedia (Wikimedia Foundation, Inc., San Francisco, CA) is a free online encyclopedia and has 4,704,035 articles in English (as of January 25, 2015). Any individual can edit articles on any topic, although in practice the number of contributors compared to users is quite small.[18] It is neither medical- nor oncology-specific in its content. Initially, based on several high-profile inaccuracies mostly pertaining to malicious individuals or state actors, there was skepticism about the accuracy and reliability of Wikipedia as a knowledge source.[19] Outside of this concern over factual inaccuracy, concerns about incompleteness, especially in the medical arena, have also persisted.[20] For example, a study comparing Wikipedia to the Medscape Drug Reference in 2008 found a

lack of information such as dosing (0% versus 90%, respectively). However, several recent studies have demonstrated that Wikipedia has markedly improved with regards to health information. In 2014, Kräenbring et al systematically compared the accuracy and completeness of drug information in the German and English language versions of Wikipedia to several standard pharmacology textbooks. They found that the accuracy of the drug information in Wikipedia was 99.7% ± 0.2% when compared with the textbook data.[22] Completeness was less robust but still reasonable, at 85%. To our knowledge, no published article has systematically addressed the information content of clinician-oriented, cancer-related articles in Wikipedia (patient-oriented content has previously been examined).[23] Some have suggested that medical Wikipedia articles be subject to formal peer review,[24] although this is unlikely to become commonplace. Given the uneven content coverage and the lack of editorial controls, answers from Wikipedia for clinical queries would likely need cross-validation from other sources to be accepted confidently.

ClinicalTrials.gov

As opposed to the resources described above, which are primarily educational, ClinicalTrials.gov is devoted to the identification of clinical trials. At first a voluntary registry, registration for most types of clinical trials became mandatory after the passing of Section 801 of the U.S. Food and Drug Administration Amendments Act of 2007 on September 27, 2007. Once a trial is registered, it is given a National Clinical Trials (NCT) number that can then be used to trace the trial's status and associated published results. With some practice, a clinician or patient user can quickly locate open trials by region, and scan at least the basic eligibility criteria. Less robust are the "results" section of each trial, although an notice of proposed rule making was recently issued to encourage more transparent reporting of trial results.[25] Thus, this portal will become increasingly useful to practicing oncologists both as a means of identifying clinical trials outside of their home institution and learning about results of completed trials.

ONCOLOGY-SPECIFIC WEBSITES
American Society of Clinical Oncology Websites

Founded in 1964, the American Society of Clinical Oncology (ASCO) represents more than 35,000 members, making it the largest professional organization representing medical oncologists. In addition to its mission statement of "conquering cancer through research, education, prevention and delivery of high-quality patient care," ASCO has been a proponent of adopting technology solutions, including the Web, to fulfil its vision.[26] Along with portals to its well-known journals, the *Journal of Clinical Oncology* and the *Journal of Oncology Practice*, ASCO has several Web-based initiatives of interest to practicing oncologists.

ASCO Connection (connection.asco.org). This multimedia, professional networking portal includes a commentary blog written by many well-known oncologists; links to the *ASCO Connection* magazine; a number of discussion groups on specific topics; forums designed to foster interactive conversations; and a number of resources specifically for trainee and early-career oncologists.

ASCO University (university.asco.org). This learning portal was established "to provide a comprehensive eLearning Center that supports lifelong learning."[27] The target audience is oncology professionals, and topics are organized by cancer type as well as by goal of the audience: continuing medical education, maintenance of certification, and ASCO's self-study publication for board examinations, *ASCO-SEP*. The site also contains the Meeting Library from past ASCO meetings, an embedded bookstore, and a link to *Journal of Clinical Oncology*'s career center.

Cancer.Net (cancer.net). Although Cancer.Net is focused toward patients and their caregivers, it contains a wealth of information that could be of use for patient education materials. The site recently underwent a complete redesign and is now very user friendly. In addition to links to factual information on the diagnosis and treatment of 124 types of cancer and cancer syndromes, the site contains multimedia content and an active blog. Content is reviewed and approved by an appointed editorial board.

Institute for Quality (instituteforquality.org). This recently debuted website consolidates ASCO's multiple quality improvement efforts into one portal. This includes the Quality Oncology Practice Initiative (commonly known as QOPI®), templates for chemotherapy planning and summarization, and clinical practice guidelines. The latter area in particular is undergoing rapid growth, aided by a collaborative wiki site, the ASCO Guidelines Wiki. Housed within the Institute but also distinct is CancerLinQ™ (cancerlinq.org), which will take on increasing relevance as the project goes live later in 2015.[28]

ALLIED ORGANIZATIONS' SITES

ASCO is but one stakeholder in the very large space of clinical oncology, and there are many others. Although an exhaustive overview of resources offered by allied organizations is out of scope of this article, we provide Table 1 as an overview of some of the major allied organizations. All of these organizations have educational resources available through their websites, with varying applicability to various practice environments. A more extensive list, including subspecialty organizations, can be found online at hemonc.org/wiki/Professional_organizations.

UNAFFILIATED SITES

There are many efforts by individuals, institutions, and other collaborations that aim to bring oncology information to

TABLE 1. Major Organizations with Content Useful to Practicing Oncologists

Organization Name	Acronym	URL	Notes
American Cancer Society	ACS	cancer.org	
American College of Surgeons	AcoS	facs.org	Includes the Commission on Cancer and the National Cancer Data Base
American Joint Committee on Cancer	AJCC	cancerstaging.org	Staging rules for most solid and some hematologic malignancies
American Society for Radiation Oncology	ASTRO	astro.org	
American Society of Hematology	ASH	hematology.org	ASH Image Bank; access to ASH proceedings
Centers for Disease Control and Prevention	CDC	cdc.gov/cancer	Information about cancer statistics and more
College of American Pathologists	CAP	cap.org	Resources about genomics and molecular medicine
European Hematology Association	EHA	ehaweb.org	Free online access to EHA proceedings
European Society for Medical Oncology	ESMO	esmo.org	Free online access to ESMO proceedings
National Cancer Institute at the National Institutes of Health	NCI	cancer.gov	
National Comprehensive Cancer Network	NCCN	nccn.org	Extensive set of regularly updated guidelines for most cancer subtypes
Oncology Nursing Society	ONS	ons.org	
Radiological Society of North America	RSNA	rsna.org	

practitioners. Unfortunately, oftentimes the result is a needless duplication of effort. Here, we focus on a few mostly not-for-profit endeavors that offer a fairly unique, extensive, or centralized source of information.

HemOnc.org

This knowledge base for chemotherapy regimens and antineoplastic drugs began 2011 as a freely available collaborative resource for oncologists and oncology professionals. Similar to Wikipedia, users can edit, create, and delete pages at will. Unlike Wikipedia, an additional stipulation that users be oncology professionals is required; there are currently 26 users with editing privileges. As of this writing, there are 1,390 chemotherapy regimens (1,865 when including variants) covering 70 benign and malignant disease conditions. To our knowledge, HemOnc.org is the largest freely

FIGURE 3. A Screenshot from HemOnc.org of R-CHOP for Untreated Follicular Lymphoma[35]

For each regimen variant, a table has a link directly to the original published article and links to comparator regimens in the case of randomized trials (as shown here). Level of evidence and comparative efficacy as reported in the original literature (for randomized trials) are shown using a simple green-yellow-red schema. Below this table, the regimen details are shown with links to individual drug pages for each drug. When relevant, additional links to external sites are provided, such as the link to the ASCO guidelines for the use of G-CSF. Not shown are five additional R-CHOP variants, 10 references to the original studies, and two references to updates of the original studies.

TABLE 2. Calculators, Dosing, and Conversion Tools

Name	URL	Description	Access Restrictions
Adjuvant Online	adjuvantonline.com/index.jsp	"…to help health professionals and patients with early cancer discuss the risks and benefits of getting additional therapy…"	Requires registration of free account
BloodRef.com	bloodref.com	Summary of key diagnostic, scoring, and prognostic systems relevant to hematology	Free to use
Body surface area calculator	www-users.med.cornell.edu/~spon/picu/calc/bsacalc.htm	Calculates BSA using DuBois and DuBois formula	Free to use
CancerMath.net	cancer.lifemath.net	Clinical outcomes calculators for breast, colon, head and neck, melanoma, and renal cancer	Free to use
ePocrates	epocrates.com	Several medical calculators, some oncology-specific	Free with installation of ePocrates
ePrognosis	eprognosis.ucsf.edu	Estimate prognosis for elders (not cancer-specific)	Free to use
Fox Chase Cancer Center nomograms	labs.fccc.edu/nomograms/	Nomograms for a variety of genitourinary cancers	Free to use with acceptance of agreement
Geriatric Assessment Tools	www.healthcare.uiowa.edu/igec/tools/	A collection of calculators relevant to geriatric patients (e.g., fall risk, weight loss, etc.)	Free to use
GlobalRPh Medical Calculators	globalrph.com/medcalcs.htm	A large collection of calculators mostly concerning dosing and laboratory parameters	Free to use
Knight Cancer Institute Cancer Survivor Predication Calculator	skynet.ohsu.edu/nomograms/	Cancer survival prediction calculators for a variety of cancer types	Free to use
Life Expectancy Calculator	socialsecurity.gov/OACT/population/longevity.html	Calculator shows the average number of additional years a person can expect to live, based only on the gender and date of birth you enter (USA only)	Free to use
MCW Health Calculators	.mcw.edu/MCW-Health-Calculators.htm	A small collection of calculators, two relevant to oncology: BMI and eGFR	Free to use
MD Anderson Clinical Calculators	mdanderson.org/education-and-research/resources-for-professionals/clinical-tools-and-resources/clinical-calculators/index.html	Nomograms for breast, colorectal, esophageal, and pancreatic cancer	Free to use
MDCalc	mdcalc.com	A large collection of calculators that are organized by specialty and system	Free to use
Medal	medal.org	"The largest international knowledge base of medical algorithms and computational procedures for medical diagnosis, treatment and administration"	Requires registration of free account
Medscape	reference.Medscape.com/guide/medical-calculators	A large collection of calculators, some of which are hematology specific	Free to use
Melanoma prediction tool	melanomaprognosis.org/	Individualized melanoma patient outcome predictions, based on the American Joint Committee of Cancer Melanoma Database	Free to use
Memorial Sloan Kettering Cancer Center prediction tools	mskcc.org/nomograms	A large number of nomograms for varying solid tumor types	Free to use with acceptance of disclaimer
QxMD	qxmd.com/calculate-online/hematology	A large collection of calculators that are organized by specialty. Also available as apps	Free to use
Stanford BMT Calculators	bmt.stanford.edu/calculators	A small collection of calculators: BSA, date from transplant, and height/weight conversions	Free to use
WolframAlpha	https://www.wolframalpha.com/	A general computational knowledge engine that does unit conversions in addition to many other things	Free to use

available chemotherapy regimen resource and has been evaluated as highly usable and relevant by its users.[29] HemOnc.org also contains extensive information on 439 chemotherapeutic or supportive medications, 127 of which are in clinical trials. New content and functionality is constantly being added; an example of a recent enhancement is shown in Fig. 3.

ChemoRegimen.com and Cancer Therapy Advisor

ChemoRegimen.com is also a freely available source of chemotherapy regimen information. However, the site partnered with Monthly Prescribing Reference (Haymarket Media, London, United Kingdom) in 2008, and new content has not been added since that time. It is thus increasingly out of date, although it does include many commonly used regi-

mens with references to the original article(s). Another site also owned by Haymarket Media is Cancer Therapy Advisor (cancertherapyadvisor.com).

MyCancerGenome.org

MyCancerGenome.org was established in 2011 by the Vanderbilt-Ingram Cancer Center as part of their personalized cancer medicine initiative.[30,31] The goal is to provide a portal for genotype-specific cancer information, along with links to genotype-directed clinical trials. The site contains extensive information on 21 types of cancer and many associated genes; it is regularly visited by a worldwide audience. The content of MyCancerGenome.org is now licensed through GenomOncology LLP (Cleveland, OH).

Oncolink.org

This website was established by the University of Pennsylvania in 1994 and contains a wealth of information that is primarily patient-oriented. However, there are also some useful resources for the practicing oncologist, including links to continuing medical education activities and prebuilt teaching sheet bundles for common chemotherapy regimens.

eHealth Initiative (ehidc.org)

This is a nonprofit organization "that brings together leaders from across the healthcare industry."[32] Among other efforts, they maintain a Cancer Resource Guide. This useful list includes tools for decision making, education, treatment management, social support, and lifestyle management. It is regularly updated.

Online Calculators

In addition to the more extensive sites described above, there are many purpose-built resources such as online calculators for diagnosis, prognosis, chemotherapy dosing, and other areas that may be of interest to the practicing oncologist. Some sites, for example, Cleveland Clinic's R-Calc (r-calc.com) let

users create their own nomograms through a simple interface. Table 2 lists several of these resources.

SOCIAL MEDIA

The implications of social media for the practicing oncologist are just beginning to be realized. These include both the benefit of networking with colleagues as well as the challenge of presenting a professional identity and of interacting with patients in this arena. Tips on how to best use social media and links to some of the most important social media outlets can be found on the ASCO social media microsite (asco.org/about-asco/social-media). Table 3 lists the social media portals likely to be of most interest to practicing oncologists. Note that in distinction from the previously mentioned resources, a majority of these sites are for-profit, although a majority are also free to join, with some (notably LinkedIn) providing a "basic" and "premier" access tier. A recent content analysis of health-related content on Facebook raises a red flag: the most common type of page (32.2% of results) was marketing or promotional.[33] Another study of Twitter prostate and breast cancer communities (defined through the social relationships of community members) found that health organizations and news media, despite their focus on health, did not play a significant role in the core communities, suggesting a disconnect between patients and practitioners.[34] It is not clear at this time which of these many social media outlets will become the "preferred" site for oncologists, and whether oncology-specific social media outlets will emerge.

CONCLUSION

As the complexity of cancer care accelerates, the need for knowledge has never been greater. Fortunately, the Internet offers a wealth of knowledge. In fact, the problem is not a lack of information but the ability to quickly identify the best

TABLE 3. Social Media Outlets of Interest to Practicing Oncologists

Website	URL	Notes
doc2doc	doc2doc.bmj.com	A community of doctors and health care providers run by the British Medical Journal
Doximity	doximity.com	Claims 50% of U.S. doctors are verified members; the single largest physician-specific social network
ecancer.org	ecancer.org	Claims to be "the leading oncology channel;" mainly a source of oncology news with some social media features
Facebook	facebook.com	The world's largest social network
Google+	plus.google.com	Social networking by Google
Linkedin	linkedin.com	The world's largest professional network; hosts many oncology-specific groups
OncLive	onclive.com	"Bringing the Oncology Community Together"
Ozmosis	ozmosis.org	In addition to social networking, the site also provides "virtual grand rounds," "clinical cases," and "journal club"
ResearchGate	researchgate.net	Mission is stated as "to connect researchers and make it easy for them to share and access scientific output, knowledge, and expertise"
SERMO	sermo.com	Claims 40% of U.S. doctors are verified members. They focus on allowing anonymous discussions between physicians.
Storify	storify.com/ASCO	ASCO-curated social media stories
Twitter	twitter.com/	The world's largest microblogging platform; dedicated community of cancer clinicians
YouTube	youtube.com/	Many cancer-specific videos; has some rudimentary networking capacity

sources of information and how to derive wisdom from the content. It is clear from the vast size of the Internet that we are all life-long learners, and the challenge is to acquire "just-in-time" information so that we can provide the best possible care to our patients. The resources that we have presented in this article should help the practicing oncologist continue along the path of information to knowledge to wisdom.

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The author(s) indicated no potential conflicts of interest.

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Using Social Media to Learn and Communicate: It Is Not About the Tweet

Michael A. Thompson, MD, PhD

OVERVIEW

Social media can be defined as the use of media to interact with social networks. Social media is not about the content of the tweet, inasmuch as the technologies and social media platforms influence how content is generated, disseminated, and used. Social media is not dead, but rather it offers rapid incoming and outgoing forms of communication, which may be utilized in a variety of "use cases" in medicine and oncology.

The prominent social media–savvy physician Bryan Vartabedian, MD, FAAP (@Doctor_V) asked, "Is Social Media Over?" on his blog, 33charts.[1] To that provocative title he added, "Or is it just part of the background?" suggesting that the novelty of social media is wearing off and that invited talks or expert opinion on "social media" may be reaching a decline. Just as we do not have American Society of Clinical Oncology (ASCO) Education Sessions on "What Is Email?" we may now focus less on the communication tool itself and more on the content and contextualization. We understand that educational content reaches us by multiple mechanisms including social media. Also, many of us are now able to interact with social media rather than just consume it. In another post titled, "Social Media Has Been Introduced to Physicians,"[2] Vartabedian noted several salient points:

- "At some point we must go beyond the introduction and into application."
- "Repeatedly pitching the terminally skeptical does not work."
- "While newbie public physicians need to be educated, there are great resources available."
- "We've reached a point where social media is now part of the professional workflow."
- "The genuinely curious and motivated will figure it out just like we did."

With this in mind, I will not over elaborate on what social media is or why physicians should use it, but rather focus on social media use cases. I would suggest to my social media–using colleagues that instead of "the cocktail party [being] over,"[3] social media use by physicians is just starting to get interesting.

WHAT IS SOCIAL MEDIA?

Social media is not a "thing" that has reached an endpoint. Rather, it is a constellation of processes. Some old and tired, some new and failing, and some already well interwoven into our digital lives. Social media is not a monomorphic phenomenon. It consists of a spectrum of the most trivial human interests as well as news, highly curated thoughts, and small and large communities.

I have previously discussed that "Social Media is a Form of Media,"[4] and that social media represents tools that may be used to store and deliver information and content disseminated through social interactions or networks. Social media includes various forms such as Facebook, blogs (e.g., ASCO Connection), forums (e.g., Doximity, Sermo, HealthTap), LinkedIn, image/video (e.g., YouTube, Vine, Instagram, SnapChat), and Twitter. There is increasing blurring between these various tools, and the social media platforms have evolved and will continue to evolve. They will not be the same years from now.

Social media differs from "traditional" media in several respects. Social media is generally faster, permanent (archived), interactive, and searchable. In addition, the conversations that emerge around a specific topic or piece of content on social media means that there can be amplified effect beyond the initial "broadcast" audience. Different social media tools may be more appropriate for various venues. My favorite social media platform is Twitter, so that is where I will focus. However, others have used video, blogs, and other social media effectively.

Social media is no longer new. We have moved beyond the early adopter phase in medicine. At previous ASCO and other meetings, a group of social media proponents have promulgated signing up and using social media. At the 2014 ASCO Annual Meeting (hashtag #ASCO14), cancer advocates noted that their lung cancer hashtag (#LCSM) was not being promoted by ASCO via its social media URL

TABLE 1. Social Media "How To" Resources

Title	Author(s) (Date)	Link
Medicine and Social Media: Why Do I Tweet?	Younes A (June 15, 2009)	http://ow.ly/sUILO
The Evolving Role of Healthcare Professionals	Katz M (October 20, 2011)	http://ow.ly/xcaKk
Getting Started in Social Media—What to Do Before You Join	Katz M (April 28, 2014)	http://ow.ly/lHi6q
Twitter 101: Signing Up—A Tutorial for Oncologists	Katz M (May 4, 2014)	http://ow.ly/xc8Wq
Twitter 102: Account Settings—A Tutorial for Oncologists	Katz M (May 5, 2014)	http://ow.ly/xc8MO
Twitter 103: Trolls, Malware & Spam—A Tutorial for Oncologists	Katz M (May 5, 2014)	http://ow.ly/xc7OA
Internet, Social Media, Privacy Regulations, and Clinical Trials	Bogler O, Thompson MA, Miller RS (June 2, 2014)	http://ow.ly/xEy8f
Social Media & Academic Oncology-Challenges and Opportunities	Katz M (December 19, 2014)	http://slidesha.re/1Jqa6B0

(www.asco.org/about-asco/social-media) and by designated social media curators. To me, this was an inflection point transitioning from early users "pushing" social media use to a milieu where a broader community could "demand" use and recognition on social media. Many didactic and pragmatic reviews of social media in medicine are available.[5,6] A few useful slides and posts from Matthew Katz, MD (@subatomicdoc) and others can help the social media beginner and are provided in Table 1. In addition, a group of ASCO staff and members of the ASCO Integrated Media and Technology Committee developed the "Ten Tips for Use of Social Media," a resource available at www.asco.org.

WHY SOCIAL MEDIA?

Physician use of social media is increasing. Reid et al[7] reviewed cancer-specific Twitter conversations among physicians and found a growing number of Twitter conversations about oncology among doctors, and some have suggested "Every Young Physician Should Have a Professional Twitter Account."[8] Some physicians adopted social media long ago, others never will, and many physicians, hematologists, and oncologists who have joined social media networks are looking for the next step.

Farris Timimi, MD, at the Mayo Clinic Center for Social Media noted "In medicine, comprehension is more critical than content." This is important for patients and for sharing between health care professionals. Herein, we'll review some "use cases" for social media.

USE: INCREASE SIGNAL-TO-NOISE RATIO

Information exchange via social media is often faster than traditional media sources including online news channels.

KEY POINTS

- Social media is a form of media.
- Social media is not dead.
- Social media offers rapid incoming and outgoing forms of communication.
- Twitter and other forms of social media are tools.
- Tools are only tools if they are useful.

However, the information on social media can be overwhelming. Choosing sources to follow, including Twitter users that create context for content, is one method. Katz et al have created an oncology/cancer hashtag system or ontology, allowing users to watch one specific topic and avoid the overwhelming crush of irrelevant content, thereby boosting the signal-to-noise ratio.[9-14] This may be especially helpful when the cancer type is not obvious in the title of a publication or for cross-disciplinary posts such as Cardio-Oncology (#CardioOnc).

These hashtags were in widespread use at the 2014 ASCO Annual Meeting (e.g., #bcsm for breast cancer social media). Boolean searches (with an implied "AND"), such as #ASCO14 #bcsm, can find #bcsm tweets at the 2014 ASCO Annual Meeting. This can help track conversations about topics over time. According to Katz, "Twitter may be relevant to how effective professional societies are at sharing research and the organizational mission."[15] Another example of improving social media content delivery came from Ekins and Perlstein in "Ten Simple Rules of Live Tweeting at Scientific Conferences."[16]

There is a suggestion that physician social networks may be more effective than medical journals at spreading information about clinical decision making.[17] However, a randomized trial of social media published in *Circulation* seemed contrary to that conclusion, suggesting that a journal's use of social media did not increase views to a given article.[18] Christian Assad-Kottner, MD, countered that conclusion by noting "Social Media is not about just posting, sharing and retweeting. There are many variables that play an important role on how social media would impact a particular outcome," and that "We live in an empowering world, with intelligent patients that also want to learn about medical advances and many are more than fit to understand our articles even without a medical degree, this I guarantee."[19]

Some have remarked "If [William] Osler were alive today, we're confident he'd be on Twitter."[20] Dr. Meyskens noted in his ASCO Connection blog post "White Coat Conversations" that he had "deep concern about the disappearing 'physician scientist'" and "I became aware that to move forward, I needed to be engaged in the national dialogue."[21] Others have asked, "Are physicians obligated to share their knowledge online?"[22] This may be critical in creating useful information

about public health issues such as vaccinations as well as understanding the risk/benefit of cancer screening, the complexities of cancer treatments, the role of research in medicine, and end-of-life decisions. In contrast, many physicians feel, regarding doctors and social media, we are "damned if you engage, damned if you do not."[23]

USE: EDUCATION NETWORKS

Beyond annual conferences and peer-to-peer communication, social media has a potential role in informing patients, families, and the public about hematology and oncology. At the 2012 American Society of Hematology (ASH) Annual Meeting and Exposition, Matthias Weiss, MD, and colleagues in the National Cancer Institute (NCI) Myeloma Steering Committee Accrual Working Group described the substantial barriers to accrual to NCI-sponsored clinical trials on multiple myeloma,[24] and subsequently identified strategies to overcome those barriers at the 2013 ASCO Annual Meeting.[25] One of those strategies was to "educate patients and providers about the significance of a new [clinical trial] using social media." Cynthia Chmielewski (@myelomateacher) and I developed the #mmsm (multiple myeloma social media) Twitter discussion group based on the example of the breast cancer social media (#bcsm) and other groups. Over the past 2 years, the following discussions have occurred at our group:

- September 15, 2013: Online patient resources and smoldering multiple myeloma (@VincentRK and @Myeloma_Doc)
- October 20, 2013: Induction; VRd versus CfzRd (@myelomaMD)
- November 16, 2013: ECOG-ACRIN Meeting (@mtmdphd)
- January 26, 2014: Allogeneic stem cell transplant in myeloma (@phari)
- February 23, 2014: Racial disparities in multiple myeloma (@VincentRK)
- March 16, 2014: Clinical trials in multiple myeloma (@Myelomateacher)
- May 18, 2014: Can we cure multiple myeloma? (@Rfonsi1)
- June 29, 2014: Amyloidosis (@brendanweiss)
- July 27, 2014: Minimal residual disease (@DrOlaLandren)
- August 24, 2014: Multiple myeloma risk assessment (@szusmani; transcript available at: ow.ly/AKVTJ)
- September 7, 2014: Crowdfunding for multiple myeloma research (@mpatientmyeloma)
- November 23, 2014: Advocating for yourself and others (@MyelomaTeacher)

Mrs. Chmielewski and I moderate and facilitate the health care provider, patient, and advocate discussions. Further information on how this started can be found on the ASCO Connection blog.[26] Many patients with multiple myeloma and thought leaders on this disease have contributed to questions and discussions in a rapid push/pull of information exchange. This would be difficult to perform with the same input and availability before social media.

This, in part, may explain why physician conversations about multiple myeloma on Twitter more than quadrupled between 2012 and 2013.[27] Many other disease-specific support groups use Twitter or Facebook to communicate. A Facebook example is the page run by Dana Holmes titled, "Asymptomatic 'Smoldering' Multiple Myeloma 'aka'-SMM – Information Exchange."[28] Although clinicians cannot participate in every online discussion group (and may not want to participate in any), knowing they exist and what information is exchanged can be enlightening. Many patients and advocates are highly educated, highly informed, and can help drive public perspective, funding, and clinical trial accrual.

USE: CROWDSOURCING/CROWDFUNDING

A group of highly informed patients (i.e., crowd) may help brainstorm ideas (i.e., source) for drug development including clinical trials (i.e., crowdsourcing). Additionally, patients and the public may help fund research by crowdfunding. The concept of "Can We Build A Kickstarter For Cancer?" has been explored by *Forbes* as a way of funding a "virtual biotech" for a single patient.[29] *Oncology Times* also asked, "Should clinical trials be crowdsourced?"[29] and *The Lancet Oncology* looked at "#trial: clinical research in the age of social media."[31]

Although not everyone is ready for these concepts, especially those with established research funding via traditional mechanisms, engaging with patient communities can help us understand the patient perspective. An educated and engaged public (via social media and in real life) is necessary to sustain a national clinical trials infrastructure. This has been embraced by the clinical trial cooperative group Alliance for Clinical Trials in Oncology (@ALLIANCE_Org; #AllianceNCTN) to crowdsource its cancer clinical trial concepts from the general public.[32]

The generalizability and utility of such social media efforts will become clearer over time. Other medical crowdfunding sites include Experiment, MedStartr, and (the now dead?) Petridish. A patient advocate–central model of crowdfunding with crowdsourced ideas vetted/curated by scientific and patient advisory boards is underway with the Myeloma Crowd Research Initiative (MCRI, www.myelomacrowd.org/mcri/). This hybrid approach may allow new ideas with thought-leader input.

USE: COLLABORATION

Although patients may share medical information on social media without legal ramifications, patient confidentiality complicates discussions among professionals. We lack a strong Health Insurance Portability and Accountability Act (HIPAA)-compliant mechanism for open online multidisciplinary conferences/clinics (MDCs). For rare tumor types, physicians have gone social with older media, such as the 2013 ASCO Annual Meeting presentation "A Model for Multi-Institutional, Multidisciplinary Sarcoma Videoconferencing."[33] At an institutional level, options include proprietary applications such as Yammer or corporate email with possible encryption. HIPAA-compliant online discussion fo-

rums are available, including from Doximity, to allow only authenticated users.

In a recent YouTube video, Linda Burns, MD, (former ASH president) reviewed a collaborative tool called MedTing (http://medting.com/).[34] MedTing is used by Best Doctors for internal use,[35] but was previously used throughout Spain to share patient case discussions. It is now being used by various groups to micro-crowdsource information exchange among selected experts (i.e., micro), forming the components of an online MDC with time- and location-shifting ability. This means not everyone needs to be in the same place and online at the same time—one limitation of current in-real-life videoconferencing either locally or nationally. This reveals likely untapped potential to extend MDCs and further enable peer-to-peer case questions such as ASH's "Ask a Hematologist" (www.hematology.org/Thehematologist/Ask/) or "Consult a Colleague" (www.hematology.org/Clinicians/Consult.aspx) features. The ASCO membership directory (www.asco.org/membership-directory) may be used for colleague contact information, and ASCO Connection Forums allow for online tumor boards, such as the "ROS1 Rearrangement: Molecular Oncology Tumor Boards."[36]

USE: PROMOTION

Many individuals, hospitals, and other groups use social media to promote myriad business interests such as increasing referrals to a private practice or to a second opinion program, raising awareness of a cancer center, or disseminating disease-specific or general cancer information. The NCI Clinical Trials Network (NCTN) groups have used social media to share annual meeting information, clinical trial information, and educational resources.

Institutions have embraced social media with various levels of enthusiasm, engagement, and effectiveness. Some push promotional information derived from other marketing materials, whereas others have an active and vibrant online presence. The best efforts engage in interactive discussions and highlight their faculty and staff.

The pharmaceutical industry has for the most part moved slowly into social media, but interest has increased since the release of some U.S. Food and Drug Administration guidance on the use of social media.[37,38] A noncomprehensive listing of entities and examples of specific uses, including some with multiple channels used for very specific purposes by a given entity (e.g., NCI), are shown in Table 2. By following users or hashtags, either individually or by combining Boolean searches, one can filter the near infinite volume of information down to something usable.

Social media is not perfect and not every platform is ideal for every use, but using social media can add a valuable com-

TABLE 2. Examples of Oncology Twitter Usernames and Hashtags

Entity	Examples
Advocacy	@AmericanCancer, @LLSAdvocacy, @myelomacrowd
ASCO	@ASCO, #ASCO15, @ASCOPost, @iConquerCancer
ASH	@ASH_hematology, @ASHClinicalNews
Cancer centers	@MDAndersonGifts, @MDAndersonLib, @MDAndersonNews, @MDAnderson_POE, @MDAndersonTrial
Disease focus	@MayoLymphoma, @MayoMyeloma
FDA	@US_FDA
Hospital system	@Aurora_Cancer, @Aurora_Health
Journals	@JAMAOnc, #JCO, #JCO, @NEJM
NCI	@theNCI, @NCICancerCtrl, @NCIMedia, @NCIprevention, @NCI_NCIP, @NCIBiospecimens, @NCISymptomMgmt @NCIGlobalHealth
NCTN	@ALLIANCE_Org, #AllianceNCTN, @EAOnc, #EAOnc, @GOG, @nrgonc, #nrgoncology, @SWOG, #SWOGOnc, #CCDR, #NCORP
News	@CancerTodayMag, @OncologyTimes
People	@DrDonSDizon, @hemoncwarner, @rschilsky, @rsm2800, @scientre
Pharmaceutical industry	@Novartis, @NVSOncoCareers, @NovartisPharma, @NovartisScience
Universities	@StanfordCancer, @uw_medicine

Abbreviations: ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; FDA, U.S. Food and Drug Administration; NCI, National Cancer Institute; NCTN, NCI National Clinical Trials Network.

plement to learning and communicating about hematology and oncology. Just following @ASCO, @theNCI, and @US_FDA would provide low tweet volume and highly informative content.

CONCLUSION

Social media is a growing form of health communication and is still evolving. Social media offers rapid incoming and outgoing forms of communication. Twitter and other forms of social media can be valuable learning and information-sharing tools. However, these tools are only helpful if they are found useful by the user. A book chapter or lecture can not determine that. Only you can. Find a social media mentor and see what you can learn.

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The Past, Present, and Future of Patient-Reported Outcomes in Oncology

Laura E. Strong, PhD

OVERVIEW

Patient-reported outcomes capture a unique and important perspective of oncology therapy. Surveys to properly capture patient-reported outcome measures have been under development for more than 2 decades. More recent efforts to understand the clinical significance of patient-reported outcomes, called performance measures, are underway. Patient-reported outcomes can be used in a variety of ways, including therapy decisions for an individual patient, payment for treatment, research into disease progression, or new drug development. Technology has already enabled electronic systems to capture and search patient-reported outcomes and in the future will assist in capturing everyday activities, which, in combination with improved informatics to sort the meaningful and actionable information, will reduce the time commitment for both patients and providers.

Although the conversation about patient-centered medicine gained traction in the United States with the formation of the nonprofit Patient-Centered Outcomes Research Institute as part of the Affordable Care Act in 2010, the discussion was started within several organizations 2 decades ago.[1-4] These, and other, organizations have facilitated processes that allow patients to contribute their voice.

A critical step in involving patients in their care is to capture their experience, but historically this information has not been captured in a format that can be broadly useful. The U.S. Food and Drug Administration (FDA) has described four ways in which a patient's condition can be assessed:

- Patient-reported outcome (PRO)
- Clinician-reported outcome (ClinRO)
- Observer-reported outcome (ObsRO)
- Performance outcome (PerfO; e.g., timed walk test)

These assessments focus on the physical, mental, and social health of the patient and can be used to evaluate disease symptoms or adverse events caused by intervention such as drugs or surgery. The major distinction of the PRO is the direct involvement of the patient rather than indirect reporting by others. Although often thought of as symptoms or functional status, PROs can also include satisfaction with care and treatment adherence. The significance of the patient's voice in oncology has been demonstrated in studies comparing reporting of symptoms by patients and clinicians. Patient reporting of Common Terminology Criteria for Adverse Events (CTCAE) is more strongly associated with measures of daily health status than that of clinicians.[5,6] The direct potential benefits of PROs for patients include improved management of symptoms and side effects that would likely result in a higher quality of life and greater satisfaction with care providers.

Two common settings for PROs are in general clinical practice or in the FDA approval of new interventions, typically drugs. In both cases, the questionnaires used to collect PROs are generally referred to as PRO measures (PROMs). A variety of PROMs are available, from the National Institutes of Health's PRO Measurement Information System (PROMIS) to the European Organization for Research and Treatment of Cancer's QLQ-C30, which is focused on patients with cancer and has disease-specific PROMs.[7,8] The National Cancer Institute has pushed for the development of a PRO version of the CTCAE called PRO-CTCAE.[9] PROMs need to be reliable (get the same answers repeatedly), valid (measure what they are designed to measure), and sensitive/responsive (show differences between patients or within patients over time). In addition, the PROM needs to fit the specific purpose, meaning that some tools may need to be tailored to specific disease symptoms and/or stage of disease.[10] Although the FDA has provided guidance on the use of PROs to support approval, the agency has also described the disadvantages of using PROs as an endpoint in cancer drug development, which include uncertainty about the clinical significance of small changes in PROs.[11,12]

Recently, a new concept has emerged that could address questions of clinical significance: the PRO-based performance measure (PRO-PM). With funding from the Centers for Medicare & Medicaid Services, the National Quality Fo-

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rum (NQF) convened workshops of stakeholders and provided a report defining the concepts. The NQF report also provides a detailed pathway for the development of PRO-PMs starting with PROs and working through the PROMs.[13] The Quality of Care Committee of the American Society of Clinical Oncology (ASCO) has reported on their efforts to develop outcome measures for pain associated with bone metastases and postchemotherapy nausea (Table 1).[14] As these measures work through the delivery of health care, payers will likely to take an interest in measures that correlate to drug use. Although PROs have been used for drug approval in the United States, their utility in drug cost and reimbursement decisions has not been tested.[15,16] As better measures and systems are developed, the E.U. experience may provide useful insight.[17]

HOW AND WHY ARE ONCOLOGISTS USING PROs IN CLINICAL PRACTICE?

A variety of PROMs are available and the last few years have seen many of the paper-based tools translated into electronic versions, resulting in dozens of academic and commercially available electronic PRO (ePRO) systems. A comparison of 33 systems in clinical use revealed the need to consider a variety of features in selecting a solution, including ease of use by patients and providers, ability to change assessments, interpretation of results, and electronic health record integration.[18]

A review of ePROs in use in oncology clinics provided examples of their implementation.[19] Two examples of academic systems are noted here: Patient Viewpoint from Johns Hopkins, and Symptom Tracking & Reporting (STAR) Prostatectomy Project from the Memorial Sloan Kettering Cancer Center (MSKCC; Table 2). These systems can be used to manage both general patient populations and very specific goals for well-defined patient populations. In both systems, patients were able to fill out surveys via the website and monitor their progress over time, and clinicians received reports via the electronic medical record. Interestingly, the MSKCC project also provided benchmarks for patients relative to others in this narrow group. Additional features of other systems

TABLE 1. Oncology-Specific PRO-PMs Developed by the ASCO Quality of Care Committee for Pilot Testing

	Pain	Postchemotherapy Nausea
PRO	Pain	Nausea
PROM	Brief Pain Inventory, worst pain	PRO-CTCAE nausea items
PRO-PM	Proportion of patients with radiographically detected metastatic disease in a given practice with worst pain of 4	Proportion of patients receiving moderately or highly emetogenic systemic cancer treatment who experience moderate or worse nausea within a week

Abbreviations: PRO, patient-reported outcome; PM, performance measure; PROM, patient-reported outcome measures; CTCAE, Common Terminology Criteria for Adverse Events.

included sending alerts to clinicians and/or providing educational material or care advice to patients.[19]

Although the potential benefits of PROs in general practice are clear, a recent review of 24 controlled clinical trials suggests that additional work is necessary to translate PROMs into clinically meaningful and actionable tools.[20] The authors evaluated three types of outcomes from these trials: patient outcomes, health service outcomes, and processes of care, which was the most frequently studied in the trials. The authors came to the following conclusion:

"The routine use of PROMs increases the frequency of discussion of patient outcomes during consultations. In some studies, PROMs are associated with improved symptom control, increased supportive care measures, and patient satisfaction. Additional effort is required to ensure patient adherence, as well as additional support to clinicians who will respond to patient concerns and issues, with clear system guidelines in place to guide their responses. More research is required to support PROM cost-benefit in terms of patient safety, clinician burden, and health services usage."[20]

This review supports the efforts described above to develop outcome measures that properly evaluate the success or failure of PROs in changing outcomes for patients, providers, and health care systems.

KEY POINTS

- Patient-reported outcomes provide a unique and important perspective in oncology.
- PROs are used in clinical practice, including via electronic capture.
- U.S. Food and Drug Administration–approved drugs can include patient-reported outcomes in their label claims.
- Patient-reported outcomes can be used for research, including studies of disease progression.
- The future of patient-reported outcomes will include technology to help patients capture data and help providers identify the information that is meaningful and actionable.

TABLE 2. Two Examples of ePRO Systems in Use at Oncology Clinics[19]

System	Patient Viewpoint (Johns Hopkins)	STAR Prostatectomy Project (MSKCC)
Population	Treatment and survivorship	Postsurgery for radical prostatectomy
Goal	Flexible system of patient monitoring	Monitor recovery of urinary and sexual function
Survey Content	Topics and schedule chosen for patient by clinician	Urinary and sexual function and quality of life
Information to Patient	Patient can see score reports showing changes over time	Changes in function over time compared to other patients and expected improvement based on prediction model

Abbreviatons: ePRO, electronic patient-reported outcomes; STAR, Symptom Tracking & Reporting; MSKCC, Memorial Sloan Kettering Cancer Center.

HOW ARE PROs USED IN ONCOLOGY DRUG DEVELOPMENT?

PROs can be used as endpoints in oncology clinical trials, resulting in symptom improvements that may be listed in label claims of drugs approved by the FDA.

Endpoints used for FDA approval of new cancer drugs from January 1990 to November 2002 were reviewed.[21] Changes in symptoms related to tumors were responsible for 4 of 57 approvals including the use of mitoxantrone in hormone-refractory prostate cancer (HRPC), approved solely for pain relief. From January 2002 to September 2006, 6 of 70 new or revised oncology drug labels included PRO assessments.[22] These drugs included gemcitabine, imatinib, abarelix, leuprolide acetate, interferon alfa-2b, and palifermin.

While noting challenges (e.g., missing data), the FDA's Guidance to Industry in 2007, "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics," included symptom endpoints as sufficient evidence for regular approval.[23] Based on draft guidance in 2006, the FDA published a guidance document in 2009 called "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims."[12] Although an oncology-focused review is not available, an overview of the PROs in labels from 2006 to 2010 reveals that the Biologic Oncology Products and Drug Oncology Products divisions at the FDA did not grant any PRO labels claims.[24]

Separately, a review of the drug approval packages for New Molecular Entities and Biologics License Applications for drugs approved from January 2006 through December 2010 was performed to evaluate the use of PROs.[25] A total of 116 approvals across all therapeutic areas were evaluated. Although there are alternative reasons to include PROs, this review assumed that all PROs included in a drug approval package were intended for approval. Among 52 drugs for which PROs were included in pivotal studies, 28 had one or more PRO claim approved. Eight cancer drugs were "denied" PRO claims in this time period. For comparison, 18 oncology applications were submitted over the same time period.[24] Across all sectors, but specifically in oncology, the major reasons that PROs did not support claims included "fit for purpose" and study design/data quality/interpretation. As noted, providing detailed evaluations of the PROs and their use would allow sponsors to better meet FDA standards in the future.[25]

Prostate cancer provides a strong example of the use of tumor symptoms as endpoints in oncology drug development. Pain and skeletal-related events are among the major disease-related symptoms of HRPC. The supplemental approval of mitoxantrone in 1996 was for pain relief in HRPC.[21] The approval of docetaxel in 2004 was based on survival benefit as the primary endpoint. Two clinical trials comparing mitoxantrone and docetaxel with secondary endpoints of PROs were inconclusive as one study was positive and the other negative.[26,27] A review of PROs and chemotherapy in clinical trials of HRPC indicates that the PROMs were generally validated, even if they were often used as a secondary end-

point.[26] Although bisphosphonates have been approved for use in HRPC to reduce skeletal-related events, the corresponding improvement in pain did not lead to an improvement in function or quality of life, illustrating the challenges associated with these and other new agents.[21,27]

In a recent review of PROs in randomized clinical trials (RCTs) of prostate cancer from January 2004 to March 2012, the authors estimate that approximately 20% of the RCTs provided sufficient data to change clinical practice.[28] The authors compared their work to a similar review covering RCTs from 1980 to 2001 and indicate that the use of PROs in RCTs has improved. One area of improvement was that the number of trials with documentation of missing data increased from 48% to 72%. Unfortunately, only 18% of the newer trials addressed statistical treatment of the missing data. This issue reflects the concerns expressed by the FDA in the examples given above. Adding to the discussion, an organization called CONSORT (Consolidated Standards of Reporting Trials) has recently published specific recommendations to improve the reporting of RCTs that include PROs.[29]

The most recent generation of FDA-approved drugs for prostate cancer includes abiraterone, cabizataxel, enzalutamide, radium Ra 223 dichloride, and sipuleucel-T. Clinical registration trials for each of these products included PROs. Notably, the products were approved from 2010 to 2013, following release of the draft and final FDA guidance on PROs. In the United States, the FDA granted pain symptom claims based on PROs to two of the five drugs, enzalutamide and abiraterone.[30] A review has collected background information for the rejection of the remaining claims by the FDA, showing that the reasons largely overlap with those for rejections from 2006 to 2010 (e.g., validity of the instrument or missing data).[30]

ARE THERE OTHER USES FOR PROs?

In addition to providing direct benefit to patients, PROs can be used for a variety of other purposes. PROs can be captured to explore disease progression and could assist in the development of improved diagnostic tools or potentially even new interventions, including new targets for drug development. Large academic medical centers fit into this stakeholder category because they have electronic health records and often have access to existing PROMs. However, another intriguing example is Open Research Exchange, which is a collaborative project developed and run by the online patient community network PatientsLikeMe.[31,32] Their goal is to attract researchers to Open Research Exchange to develop and test health outcome measures within the patient communities of PatientsLikeMe. Although the company is for profit, the Open Research Exchange advisors include many of the leading academics involved in PROs, including Dr. Ethan Basch from the Lineberger Comprehensive Cancer Center at the University of North Carolina.

HOW CAN TECHNOLOGY HELP PATIENTS (AND PROVIDERS)?

Capturing and analyzing all of the data points for PROs can be cumbersome for providers and patients, particularly when the patients are experiencing decreased function as a result of disease or intervention. One of the negative consequences of this is the disadvantage of missing data noted above. The move from paper to electronic PROs has increased the flexibility of data capture. However, even seemingly small changes such as having patients use their own device rather than a device provided specifically for filling out the PROs can potentially influence results.[33]

In the future, technology may provide a means for everyday activities (performance outcomes) to essentially be captured as PROs. As an example, consider two common symptoms experienced by patients with cancer: fatigue and depression. For fatigue, PROMs ask questions about feelings of being run down, tired, or lacking energy. Alternatively, a wearable device or mobile application on a smartphone (most of which have sensors, including accelerometers) could directly gauge the daily activity levels of patients with cancer with the appropriate health status. The simplest marketed devices collect activity data, but newer products include sensors for additional factors, such as vital signs and heart rhythms. These devices range from consumer products to FDA-cleared devices. On the consumer front, the Fitbit and Jawbone are general activity trackers, and next-generation devices have emerged with sensors for heart rate, such as the Mio Link and TomTom Runner. Although consumer devices may not be appropriate for all purposes, there are suggestions from clinical trials that wearables have utility in specific cases, such as predicting recovery from surgery.[34,35] There are also FDA-cleared sensors with greater capabilities, such as skin temperature and body posture. For example, HealthPatch MD from Vital Connect and wGT3X-BT Monitor from ActiGraph have recently been tested for utility in clinical trials.[36] If a correlation between fatigue and activity is demonstrated, the devices or apps could collect more information while decreasing the patient reporting burden.

Multiple companies, including Ginger.io, Priori, and Cross-check, are developing mobile applications (apps) for smartphones that may allow them to correlate behavior with mood as determined by traditional survey instruments. These apps are tracking general activity such as volume of text messages and phone calls, voice analysis, and location tracking.[37] Ginger.io is currently running a randomized, controlled clinical trial of their app called Mood Matters, which would provide support for exploration in other settings such as oncology.[38]

As everyday activities (performance outcomes) become be captured as PROs, there will be additional concerns to address. A few of these concerns are noted here. First, the conversion itself does not address the increased informatics workload for providers. Methods for data visualization or other dashboards that could assist in identifying what is meaningful and might guide action would address this concern. Second, the reliance on technology would likely exacerbate the gap between patients with access to technology (smartphones with data packages) and those without. Although there are strategies to address these issues, consideration should be given to differences in technology solutions that affect the comparability of results. Finally, care should be taken that the technology does not change patient behavior unless that is an intended outcome. A recent example comes from an experiment by Jawbone to encourage their users to be more active on Thanksgiving.[39] The company found that even a holiday greeting that included a suggested step count modified behavior. Technology provides tremendous potential as another way to capture the "voice" of the patient, but great care and consideration are necessary to ensure the utility of the data.

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PROFESSIONAL DEVELOPMENT

Trends, Anecdotes, and Predictions: Oncology Practices Today

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Clinical Oncology Practice 2015: Preparing for the Future

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OVERVIEW

The clinical practice of oncology has become increasingly complex. An explosion of medical knowledge, increased demands on provider time, and involved patients have changed the way many oncologists practice. What was an acceptable practice model in the past may now be relatively inefficient. This review covers three areas that address these changes. The American Society of Clinical Oncology (ASCO) National Oncology Census defines who the U.S. oncology community is, and their perceptions of how practice patterns may be changing. The National Cancer Institute (NCI)-ASCO Teams in Cancer Care Project explores how best to employ team science to improve the efficiency and quality of cancer care in the United States. Finally, how physician assistants (PAs) and nurse practitioners (NPs) might be best integrated into team-based care in oncology and the barriers to integration are reviewed.

The ASCO National Oncology Census was originally launched in 2012.[1] The goals of the National Oncology Census were to help ASCO understand where oncologists were providing services, their practice characteristics, and their challenges. Before the launch of the census, some members of ASCO voiced concerns about substantial shifts in oncology care from private practices to university- or hospital-based practices. Also, it is projected that there will be increases in the number of patients and decreases in the supply of oncologists.[2] Therefore, it was important for ASCO to try to clarify if the apparent shifts were actually occurring throughout the nation and, ultimately, whether this was affecting delivery of cancer care in United States.

For the 2014 census, there were 1,252 respondents comprised of 974 practices, representing more than 10,000 oncologists in the United States. The number of practices and oncologists represented in the 2014 National Oncology Census were much greater than the 530 practices and nearly 8,000 oncologists responding in 2013.[3]

More practices from the South and West regions of the United States responded in 2014 (Fig. 1). The largest number of respondents was from physician-owned practices, with the second highest being from hospital/health-system–owned practices, and the third being from academic practices. There were respondents from industry and those in international and government settings, as well as retired practitioners. For the purposes of analysis, we focused on the physician-owned, hospital/health-system–owned, and academic practices.

As would be expected, a majority of the practices focused on hematology and oncology services with many also providing radiation oncology, gynecology oncology, and surgical oncology. Fewer respondents were part of multidisciplinary practices that included internal medicine, gynecology, or pediatrics.

The census survey tool asked the respondents questions about plans for their practice in the next 12 months, including selling/merging their practice or buying another practice. More than 70% of respondents were unlikely to plan any major shifts in the upcoming 12 months, with only about 4% of practices planning to close or sell their practice and only about 5% planning to purchase another practice. With regards to physician-owned groups, about 6% planned to close or merge, about 7% planned to sell, and about 4% planned to purchase another practice.

Hospital/health-system–owned practices and physician-owned practices were more likely to indicate that financial pressures were because of payers, costs, competition, and drug pricing issues. Meanwhile, academic practices cited research issues, staffing issues, and competitive pressures as their most important concerns. Overall, the pressures cited by practices responding to the National Oncology Census during the past 3 years seem to focus around payer issues, cost pressures, competitive pressures, and drug pricing. The overall payer mix remains the same, with a trend toward an increasing percentage of patients on Medicaid and Medicare in 2014 compared with 2013 and 2012. The majority of the practices are still not participating in accountable care organizations. Academic practices, by far, use more advanced practice nurses and PAs (Fig. 2). Respondents also indicated that for potential layoff considerations, that administrative staff and other clinical staff are more likely to be affected in their practices (Fig. 3).

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FIGURE 1. Practices by Census Region and Practice Setting (971 patients)

FIGURE 2. Number of Advanced Practice Nurses and Physician Assistants by Practice Setting
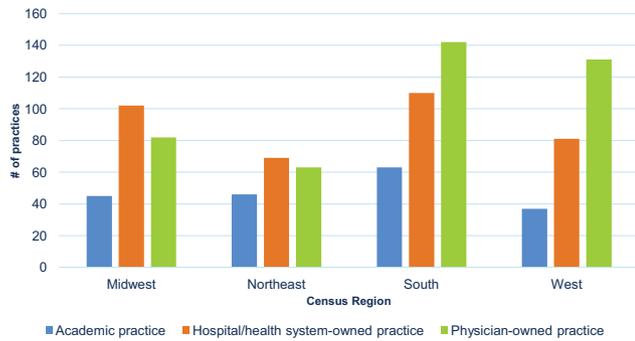
With each successive year of the ASCO National Oncology Census, it is clear that the shifts away from private practice to more alignment/consolidation or moves to hospital-based practices has occurred.[1,3] These findings seem consistent with other studies that note size growth of oncology practices.[4] Ultimately, it is unclear whether the pendulum has come to a rest or whether there will be further consolidation or shift. ASCO has already begun preparing for the 2015 census, with plans to identify additional data or sources to support and validate this census process. The information from this effort informs ASCO's work in supporting its membership, including policy efforts and shaping legislation and regulation, payment reform, and workforce needs. Ultimately, understanding the practice environment surrounding the providers who care for patients with cancer is important to ensure increasingly complex therapies are delivered to some of our most vulnerable patient populations in the United States and that all patients have access to high-quality cancer care.

KEY POINTS

- ASCO Oncology Census continues to show shifts away from private practice to more alignment/consolidation.
- Practices are concerned about payer issues, cost pressures, competitive pressures, and drug pricing.
- True team-based approaches to oncology care may provide a means of optimizing resource utilization and improving the quality of care.
- Utilization of advanced practice providers in oncology will help meet workforce needs, although significant importunities still exist to improve the engagement of providers, national organizations, and policy makers.
- Restrictive barriers in legislation, reimbursement, provider bias, and educational infrastructure reduce the benefits of utilizing advanced practice providers in oncology and inhibit the ability to expand and effectively employ advanced practice providers in the workforce.
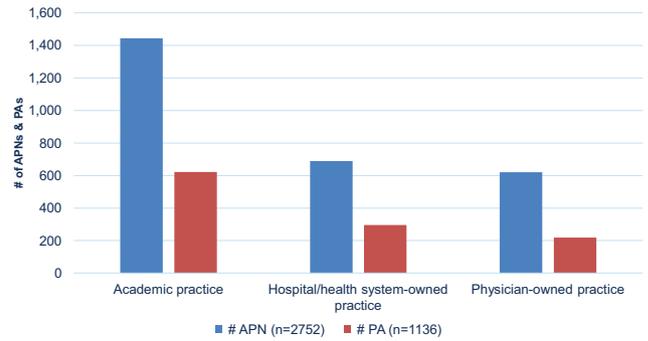
TEAM-BASED CARE IN ONCOLOGY

At the risk of sounding trite, high-quality cancer care takes a village. Multimodality therapy requires coordinated care delivery among several groups of clinicians as patients move along the continuum of cancer care—from risk assessment, prevention, diagnosis, treatment, and surveillance to survivorship and advanced cancer. Within any given clinic, increasingly complex therapies require clinicians with advanced, specialized training. Clear communication and transparent, defined roles and responsibilities help ensure that care needs are addressed and timely decisions are made. Placing prompts in electronic health records, sending reminders to patients, and requiring detailed notes at transfers of care are important strategies to improve communication. Embedding tools in the process helps address issues in the immediate, but more lasting change can come from explicitly helping to transform individual clinicians and separate groups into a team that works together.

In March 2015, the *Journal of Oncology Practice* presented an overview of cancer care team effectiveness[5] and used a case-based vignette[6] to discuss the importance of delivering cancer care as a team. These manuscripts marked the beginning of collaboration between NCI and ASCO bringing clinicians, patient advocates, and researchers together to explore application of the evidence of team effectiveness to clin-

FIGURE 3. Potential for Staff Layoffs by Year
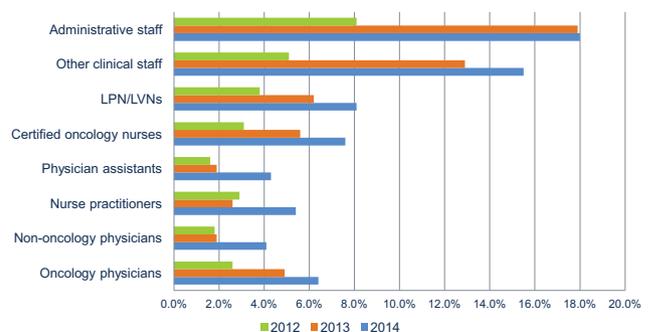
ical practice. The NCI-ASCO Teams in Cancer Care Project will unfold at a 2016 workshop.

Teams are defined as two or more people who "interact dynamically, interdependently, and adaptively" to accomplish a shared goal.[6] Weaver et al assessed the role of interprofessional teams in an inpatient oncology setting and concluded that nurses and oncologists have disparate perceptions of the effectiveness of their collaboration and work as a team.[7] In an editorial to accompany the article, Childress questioned the need for additional studies to demonstrate "significant and well-documented" differences in perception of communication.[8] Taplin et al note that communication is one of the eight hallmark traits of effective teams. The hypothesis the NCI-ASCO project will discuss is that deliberately identifying and enhancing team interactions in oncology care will help improve cancer care delivery.

This project fits in the larger context of the transformation of health care delivery and payment models. The field of primary care has actively engaged in reinventing care to form a patient-centered medical home. Experiments are underway to apply the same concepts to specialty care delivery. At the same time, public and private payers and ASCO are proposing payment models that would move away from payment based on specific procedures and physician contributions and toward an approach that provides bundled payments for comprehensive care and allows greater flexibility in how care is organized and delivered. A team-based approach has potential to leverage these changes, provide an opportunity to reexamine clinician roles and responsibilities, and may enable the most efficient delivery of high-quality health care services.

Clinicians in oncology care may believe that their practice already involves working in teams. People with cancer often view their care as a seamless experience and most likely desire this approach from the many clinicians they engage across the care continuum—from diagnosis to surgery to therapeutic radiation to chemotherapy to palliation to rehabilitation. Do clinicians meet this standard or is the responsibility more often on the patient or their caregivers to connect the dots? If clinicians saw themselves through the patient's eyes as members of a single team coordinating care, could quality, access, efficiency, and clinical outcomes improve? Should the person with cancer have an explicit role and set of responsibilities within the treatment team? If clinicians approach patients with this question, would they embrace a role in the team or believe the clinician is trying to avoid responsibility? Could working in teams with well-recognized and valued roles for all members of the team improve job satisfaction and reduce provider burnout?[9,10] These questions have many possible answers.

The literature in health care and many other fields demonstrates that effective teamwork takes time and intentional focus to nurture, develop, and sustain. To this end, it is the hope that a collaboration of clinicians involved in cancer care, advocates who have been patients, and researchers engaged in studying teams will highlight successful models and identify areas for future research. Leaders of the initiative will invite applicants to serve on writing groups to apply principles of team-based care to specific case scenarios. The writing groups will meet in person and work by conference call and email to develop a presentation for an NCI-ASCO workshop in February 2016 at the ASCO Quality Care Symposium. Presenters will engage in discussion with workshop attendees to enrich their work and submit final manuscripts for publication in the *Journal of Oncology Practice.*

ADVANCED PRACTICE PROVIDERS WORKFORCE IN ONCOLOGY

As a key member of team-based care in oncology, the use of advanced practice providers (APPs) to help meet the workforce demands has been one of the proposed solutions since the initial workforce strategic plan was approved by the ASCO Board of Directors in 2008. The utilization of APPs in oncology practices can increase practice efficiency and productivity as well as the professional satisfaction of collaborating oncologists.[11] However, the degree to which the use of APPs will help meet future demand is unclear, as the current and projected workforce of APPs in oncology has been challenging to report. Based on census data from 2013, the American Academy of Physician Assistants (AAPA) reported that there were an estimated 2,140 clinically practicing PAs in adult medical, surgical, and radiation oncology subspecialties.[12] This represented a 25% increase compared with 2010 census data.[13] However, important characteristics such as age, geographic distribution, education, years of experience, and years to expected retirement are unknown. Similar challenges are faced when trying to describe the NP workforce in oncology. The American Association of Nurse Practitioners (AANP) also publically reports survey data for licensed NPs. In 2013, of the more than 205,000 licensed NPs, approximately 2,050 worked in oncology and had been in practice for an average of 7.7 years with a median age of 48.[14]

MODELS OF APP INTEGRATION INTO TEAM-BASED CARE

There are three models of care utilizing APPs in the team-based care setting: (1) the independent-visit model (IVM) in which APPs predominantly see patients independently in clinic but still under the collaborative practice agreement with their physicians, (2) the shared-visit model (SVM), for which patients are seen by both the APP and the physician during the clinical encounter, and (3) the mixed-visit model (MVM) in which both the independent and shared visit model is utilized to manage the clinical volume but neither is the predominant encounter used.

To examine the differences between the different models, Buswell et al reported the effect of the practice models on productivity, fees, and provider and patient satisfaction in an academic cancer center.[15] They found that productivity for the IVM, MVM, and SVM, as measured by the number of new and established patients, was similar between the models

(6.8, 6.7, and 7.0 patients seen per 4-hour session, respectively). Both physician and APPs were very satisfied with the IVM and reported patient-centered and productivity-based reasons influencing the decision to use their chosen model. For the SVM, physicians were still very satisfied with the model, whereas, APPs were only moderately satisfied. Reasons for utilizing the SVM were more physician-centered, focusing on physician preferences and perceptions. Importantly, there were extremely high levels of patient satisfaction for both models (100% satisfaction with care received from either model).

In a much larger study of the private practice setting, the results of the ASCO study of collaborative practice arrangements also noted high levels of patient and provider satisfaction with the APP models.[11] The most common model in the survey was the independent model. The IVM was also 19% more productive (based on relative value units, [RVUs]) when the APP worked with the entire group of physicians as compared with an IVM when the APP worked exclusively with a limited number of physicians. However, one should be cautious to conclude that the more productive RVU model is the ideal model to utilize APPs. Further insight into measures of quality and continuity of care of the two models would be important to distinguish. In addition, RVUs as the sole productivity measure is a limited assessment of the value an APP adds to a practice. The study did not take into account the non-revenue generating activity performed for each model, which would be important in defining the preferred models.

BARRIERS TO INTEGRATION
Provider and Patient
ASCO's study of the collaborative practice arrangements of APPs identified physician lack of interest in working with APPs as the most common reason not to utilize them in their practice.[11] To determine how to best motivate attitudinal change, it is important to explore the reasons for lack of interest. As the ASCO report was primarily physician-owned private practices (73%) with only 8% surveyed in academic practice, it is possible that the lack of interest is based on the fear of decreased personal compensation for the physician. It has been shown that the private-practice model has significantly more oncologists compensated on an incentive-based model compared with academic models (39.3% vs. 3.1%; p < 0.001).[16] Therefore, it may be important to focus on the increased practice productivity when using APPs to encourage utilization in private practice. Furthermore, as a pure incentive-based model is associated with the highest rate of burnout, the increased professional satisfaction when working with APPs can be another educational point to change perceptions.

There are other challenges to incorporating APPs into clinical practice that are largely historic or based more on personal bias than fact.[17] For example, the belief that utilizing APPs will negatively affect the physician/provider relationship or that patients will not accept APPs as part of the care team is not founded. Studies have demonstrated high levels

of patient and provider satisfaction with the collaborative practice model with increased utilization nationally.[11,15,18,19] It is likely that a portion of the workforce that is nearing retirement is also the same group that has less experience and understanding of the PA and NP profession and, therefore, more perceived bias. This barrier, however, is likely to end as oncologists entering the workforce develop experience working with PAs and NPs during their fellowship. In a survey of fellowship program directors in 2011, 90% of medical directors reported that their fellows work with NPs or PAs.[20] What is not well known is how well prepared oncologists entering the workforce will be to lead a medical team that incorporates APPs. It will be important moving forward for oncologists to understand the different models for APP utilization, as well as the regulatory and reimbursement requirements to effectively lead the medical team. Ideally, this educational need could be incorporated into the fellowship training programs before entering the workforce and then further refined at the practice level based on state laws and institutional policies.

Legislative
With modern medicine should come modern legislation. Unfortunately, despite widespread acceptance of PAs and NPs, there remain substantial historic and dated legislative barriers that limit the effect that APPs have in providing quality care. Despite differences in regulations between PAs and NPs, there is common ground in the interest to ensure that PAs and NP are practicing to the highest level of their degree and professional training. Both the AANP and AAPA have written position statements and established policy priorities to improve access to health care through removing barriers in federal and state regulations. Specifically, some of the shared priorities nationally for APPs that will directly affect oncologic care include authorizing APPs to provide hospice care and allowing APPs to certify home care services and order durable medical equipment. At the state level, limitations on the prescriptive authority and scope of practice are also shared concerns between PAs and NPs. For example, 14 states still prohibit PAs from prescribing schedule II narcotics. Practice productivity is highest when APPs are used for advanced activities.[21] Therefore, by expanding the prescriptive privileges and allowing APPs to practice at the highest level of their scope of practice will help ensure that quality and efficient care will continue for patients with cancer.

To highlight the benefits of improving legislation for APPs, a study was conducted to simulate the effect that enacting policy changes would have on the supply of PAs and NPs in primary care in Alabama.[22] This simulation was based on policy changes that facilitated obtaining licensure, expanded prescriptive privileges, and removed several limitations on scope of practice. The results demonstrated the potential for substantial health care savings and increased access to care in Alabama with simple policy changes. The specific results of this study cannot be directly applied to the current and projected work demands in oncology. However, the proof of principle should be helpful to policymakers and advocacy

groups in further examining the role of utilization of APPs in oncology.

Productivity and Reimbursement

It is generally accepted that practices that incorporate APPs are more productive and efficient in providing quality care to patients than practices that do not. However, as practices work to integrate APPs into clinical practice they have been challenged with accurately assessing the productivity and value of individual APPs. Practices that utilize a system strictly based on RVUs will likely underestimate the productivity and value of APPs because of the inability to accurately measure RVUs. For example, global surgical visits and the SVM will render the time and effort of the APP invisible.[23] Even in the IVM, all incident-to visits as well as visits for many commercial payers are billed under the physician's National Provider Identifier, despite all care being provided by the APP. In addition, there are numerous activities in clinical care that APPs provide that are not billable encounters but bring quality and value to the practice. Importantly, these nonrevenue generating activities, if not completed by the APP, would have to be completed by the physician. The challenges in assessing the productivity of APPs and the limited benchmarking data available affects the ability to not only improve productivity of the APPs but will hinder the ability to increase utilization. Practices will struggle to determine when to hire new APPs and how their time should be allocated to support the clinical enterprise. Also, practice managers will inherently be unable to determine equitable compensation, comparison, and accountability of APPs within a practice.

Moving forward, it will be important for administrators and APPs to work together to ensure that productivity assessments accurately reflect the overall value that the APP brings to the care team. Options should include continued use of claims data, but also use of practice management and health records software to measure care rendered by an APP. Using a team-based approach to productivity where the physician and APP RVU are combined may be a reasonable alternative to the independent model of assessment. To augment the measurement of productivity, time and effort studies can be completed on a regular basis to track both the billable and nonbillable effort. This exercise will not only provide a greater understanding of the value of the APP, but it may highlight opportunities to improve practice efficiency and ensure that APPs are working up to the level of their degree.

In regard to reimbursement, there are several common myths and misconceptions that can stymie the expansion of APPs in oncology. Several myths such as "APPs cannot see new patients" or "APPs cannot bill above a certain level" are easily debunked with a little education and, if needed, support from the national advocacy organizations. However, one of the more challenging misconceptions is the over estimation that the 85% reimbursement rate of the APPs compared with the physician rate will have on the cost-effectiveness of APPs. Numerous studies on PAs and NPs have demonstrated that APPs are cost-effective health care

providers. This can be explained by physician salaries being consistently 30% to 50% higher than APPs, incident-to billing reimbursed at 100%, and the savings on reduced recruitment and retention costs of APPs.

Educational Systems

One of the biggest barriers to utilizing APPs to help meet the oncologic workforce demands may be in the educational infrastructure in place for the education of APPs. The education of APPs generally provides a general medical education with limited time dedicated to oncology in the curriculum. In a survey of PA programs, cancer prevention and diagnosis were the primary focus of the oncologic curriculum with no or little focus on acute management, oncologic emergencies, and supportive and survivorship care.[24] In addition, although nearly all PA programs offer locally available, elective rotations in oncology, less than 15% of students participate in such opportunities. Similarly, in a survey of the educational experience of oncology NPs, most reported being poorly prepared to provide cancer care and not at all prepared to perform oncologic procedures or manage oncologic emergencies.[25] Once APPs enter the oncologic workforce, the majority report on-the-job training through mentorship with supervising/collaborating physicians, as well as, self-study as the means to obtaining the core competencies for their position.

To overcome the educational barriers to expanding the APP workforce will require efforts both during and immediately after the graduate training of APPs. With less than 15% of students pursuing elective rotations in oncology, the current workforce of APPs in oncology should help engage students during their didactic year to increase participation. This could be done by developing relationships with local APP programs and educating students about a career in oncology. The national organizations that represent APPs in oncology should also engage new student members to help increase interest in the field. As an example, the Association of Physician Assistants in Oncology has created a student day seminar at the annual continuing medication education (CME) meeting that offers students a free day of participation in the conference, as well as seminars for students about pursuing a career in oncology.

To help APPs gain the knowledge they need to meet the demands of caring for patients with cancer will require improvements in the core curriculum in graduate education. Unfortunately, it will be hard to expand the curriculum given the limited time available during the didactic year. It is possible that a flipped-curriculum model may be helpful to meet this challenge. In this model, standardized lectures can be viewed outside of the classroom and time spent in the classroom can be used for more active learning opportunities such as teamed-based learning and skills training.[24] The active classroom time would also be another opportunity for clinical preceptors and other APPs in oncology to engage students in oncology. The core curriculum for the flipped-curriculum model could be provided through standardized programs similar to ASCO's Curricula for Advanced Practice

Provider's (ACAPP), but with a focus on expanding the core curriculum of students in current APP programs.

Once an APP enters the oncologic workforce, the majority of education occurs during on-the-job training and self-study. To help meet the educational needs of APPs, programs such as ACAPP were developed and annual CME meetings for APPs in oncology are offered. These programs help offset the burden of individual practices in onboarding new graduates and provide ongoing education to APPs in oncology. As the number of APPs in oncology continues to increase, educational providers and industry have become increas-

ingly interested in engaging this emerging market. Certainly, programs that provide certificates of completion and educational credits will be welcomed. However, educational programming for the intent of certification in oncology should be met with caution. Utilization of APPs in oncology is variable and differs in practice setting, discipline, and patient population. An individualized approach to ensuring the competency of APPs in oncology is, therefore, the best approach. Promoting the certification of APPs in oncology could be a substantial barrier to increasing the APP workforce and should not be endorsed as a requirement to practice.

Disclosures of Potential Conflicts of Interest

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SARCOMA

Adjuvant Treatment of Soft Tissue Sarcoma: What, When, and Why

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Adjuvant Chemotherapy for Soft Tissue Sarcoma

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OVERVIEW

Adjuvant chemotherapy is not standard treatment in soft tissue sarcoma (STS). However, when the risk of relapse is high, it is an option for shared decision making with the patient in conditions of uncertainty. This is because available evidence is conflicting, even if several randomized clinical trials have been performed for 4 decades and also have been pooled into meta-analyses. Indeed, available meta-analyses point to a benefit in the 5% to 10% range in terms of survival and distant relapse rate. Some local benefit also was suggested by some trials. Placing chemotherapy in the preoperative setting may help gain a local advantage in terms of the quality of surgical margins or decreased sequelae. This may be done within a personalized approach according to the clinical presentation. Attempts to personalize treatment on the basis of the variegated pathology and molecular biology of STS subgroups are ongoing as well, according to what is done in the medical treatment of advanced STS. Thus, decision making for adjuvant and neoadjuvant indications deserves personalization in clinical research and in clinical practice, taking profit from all multidisciplinary clinical skills available at a sarcoma reference center, though with a degree of subjectivity because of the limitations of available evidence.

Adult-type soft tissue sarcomas are a variegate group of malignancies. They are highly heterogeneous, because they are made up of several histologies and arise from virtually all body sites.[1] In addition, they are rare, and their incidence is approximately 4 per 100,000 per year.[2] This incidence does not prevent controlled trials, but pooling together different histologies and possibly different primary sites is often the price to pay. It is true that more than half of STS cases are high-grade and undifferentiated pleomorphic sarcomas, liposarcomas, leiomyosarcomas, myxofibrosarcomas, synovial sarcomas, or malignant peripheral nerve sheath tumors, and more than half of them arise in the limbs. However, a high degree of heterogeneity remains, even after selecting a group of patients with these types of STS, and other relevant subgroups (e.g., uterine sarcomas) are left behind. This contributes to major limitations of available evidence on adjuvant chemotherapy in STS and, thus, a considerable degree of uncertainty on its clinical value, although several randomized clinical trials have been performed in the last 40 years.

When one singles out high-grade STS, the mortality rate exceeds 50%. In addition to the malignancy grade, other main prognostic factors are size and presentation—for example, deep fascial extension. By combining these three factors, it is easy to select a population in which two-thirds of patients may die of their disease. Prognostic nomograms are available to refine the prognosis with a view toward adjuvant decisions.[3-6]

Currently, the treatment of metastatic disease is unsatisfactory. Surgery of lung metastases is the main option when secondary lesions are isolated in the lungs, and the number of such lesions is relatively low. A cure may be achieved in a minority of patients with these metastases, and the course of disease may be slowed down in a subgroup of others; however, most patients will experience relapse in a matter of months. Chemotherapy is based on anthracyclines and ifosfamide, though other cytotoxics and even molecularly targeted agents are available, which have interesting antitumor activity in selected histologies. Indeed, there is currently a trend in favor of an histology-driven approach in the medical therapy of STS. However, the effect of medical therapy in the metastatic setting is essentially palliative, though improving over the last years. The median survival of patients with metastatic disease often has been reported to be in the range of 1 year. Undoubtedly, there are subgroups who benefit from surgery of lung metastases and currently available medical therapies, but a cure is essentially precluded in most cases, and—though possibly higher than once reported— overall survival remains unsatisfactory, if one leaves aside the tails of curves.

In addition, STS often pose challenging problems regarding surgery of localized disease. In a minority of cases, one may hope to convert mutilating surgery into limb-sparing procedures by means of preoperative cytoreduction. In several other cases, cytoreduction is felt by the surgeon to be potentially useful to minimize sequelae and improve the local control rate. This is why chemotherapy is resorted to preoperatively in a proportion of patients, which may vary from an

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institution to another, with a view toward local cytoreduction, in addition to its possible systemic effects.

In conclusion, there is a huge need for effective adjuvant and/or neoadjuvant treatments in STS. The proportion of potentially amenable patients may roughly amount to one-half of cases. This applies to adult-type STS, because extraskeletal Ewing sarcomas and embryonal or alveolar rhabdomyosarcoma fall in a distinct group of sarcomas, even when they occur in the adult, which deserves chemotherapy in all cases as a key component of the standard treatment.

AVAILABLE EVIDENCE

Several randomized, controlled trials have been performed with adjuvant chemotherapy for STS, starting from the 1970s, when chemotherapy was shown to be crucial in revolutionizing the prognosis of childhood sarcomas, (i.e., osteosarcoma, Ewing sarcoma, and rhabdomyosarcoma). Trials performed in STS can be divided into two generations. First-generation trials used anthracycline-based regimens—that is, either doxorubicin alone or combinations that today would be regarded as exploiting doxorubicin as virtually the only, or nearly only, active drug. Second-generation trials have been based on combinations of anthracyclines and ifosfamide. Doses varied substantially, but at least the two main active drugs in STS were incorporated. A high degree of heterogeneity can be found in all these studies also, as far as the patient populations are concerned, and the number of patients ranged from a few dozens to hundreds.

A meta-analysis of these randomized clinical trials, published in 2008, confirmed the benefit that a previous meta-analysis, done on individual patient data, had already shown in terms of local and distant relapse rate; the 2008 publication also noted a statistically significant benefit in terms of overall

survival for doxorubicin plus ifosfamide (p = 0.01).[7,8] The magnitude of benefit was in the 5% to 10% range. Although small, this could well justify the choice of using chemotherapy in high-risk patients, and a meta-analysis of several randomized clinical trials could be regarded as sufficient evidence to back this choice. Methodologically, the last meta-analysis was not done on individual patient data. However, the main limitation of any meta-analysis of adjuvant chemotherapy in STS is that the pooled trials are conflicting, and the largest trials point to a lack of benefit. Clearly, this substantially undermines any positive conclusion. Conversely, small trials were less heterogeneous in their patient population and/or were carried out by single institutions with more expertise with the disease. In rare cancers, large trials enrolling patients from a variety of institutions with different expertise levels may pose substantial problems in terms of quality of care. Random assignment is not a guarantee that this clinical bias is offset just because it is operating in both arms, because the most effective treatment may be more penalized by shortcomings in quality of care (e.g., in the adjuvant setting, by surgical treatment).

In 2012, a large, randomized trial was published by the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group, which provided a negative result by using a regimen of doxorubicin plus ifosfamide at full doses, though the latter was given at 5 g/m^2 in 24 hours.[9] The relapse rate of the study patient population was in the 50% range; thus, it was at a level that may be slightly lower than the one selected by some positive studies. By updating the meta-analysis using aggregate data for overall survival of this and other new studies, a statistically significant benefit was still apparent in terms of survival in favor of chemotherapy (p = 0.02).

A randomized trial performed by the Italian Sarcoma Group (ISG) and the Spanish Sarcoma Group (GEIS), published in 2008, compared five cycles (three preoperatively and two postoperatively) of full-dose epirubicin (an analog of doxorubicin) plus ifosfamide with 3 preoperative cycles of the same regimen.[10] Both relapse-free survival and overall survival were superimposable, but they also were superimposable to the treatment arm (five postoperative cycles of the same regimen) of a previous randomized trial carried out by ISG that had a no-chemotherapy control arm.[11] That trial had been closed in advance because of an early major benefit in survival in favor of the adjuvant treatment arm. With a longer follow-up time, the statistical significance was lost, though a trend was preserved.[12] The patient population of the ISG trials was definitely in the high-risk group, and it was calculated that the prognosis expected without chemotherapy for patients enrolled on the most recent trial, estimated through available nomograms, was compatible with the performance of the control group in the first study. This may be taken as indirect evidence that three courses of a full-dose regimen of anthracycline plus ifosfamide can give some prognostic benefit in a truly high-risk STS patient population.

It is interesting that several trials on adjuvant chemotherapy in STS detected some benefit in terms of local relapses.[8,13]

KEY POINTS

- Adjuvant chemotherapy is not standard treatment in soft tissue sarcoma (STS), but it is an option to share with the patient in conditions of uncertainty when the risk of relapse is high.
- Controlled evidence is available, and was also pooled in meta-analyses, but its weakness is that studies have been conflicting.
- If the decision is to resort to chemotherapy in the patient with localized high-risk STS, chemotherapy can be administered preoperatively if cytoreduction is felt to help improve the quality of surgical margins and/or sequelae.
- Personalization of adjuvant chemotherapy across diverse STS subgroups is worth testing in clinical research as a way forward, to improve its efficacy.
- Personalized, rational decision making in conditions of uncertainty on adjuvant treatment for patients with STS is the every-day challenge that multidisciplinary tumor boards face at reference sarcoma centers or within sarcoma networks.

This observation is difficult to explain, especially in the presence of a questionable benefit for distant relapse. However, one should recall that the local control in some patients with high-risk STS may be challenging. In addition, some local relapses in STS may well lead to death. This might explain the differences in survival in the absence of comparable differences in distant relapses. In addition, this could add to the rationale of placing chemotherapy preoperatively, as long as the decision has been made in the single case to use it as an adjunct to surgery. The ISG trial allowed the combination of neoadjuvant chemotherapy with preoperative radiation therapy, and this proved to be tolerable in the proportion of patients in whom it was used.

With an incidence in the range of 0.5 per 100,000 per year, uterine sarcomas are a relevant subgroup in the STS family. They entail a significant risk of relapse. Leiomyosarcoma is the main subgroup, if one excludes mixed mullerian tumors (carcinosarcomas), which are currently held to be epithelial in nature. Other highly malignant subgroups are high-grade endometrial stromal sarcomas and undifferentiated uterine sarcomas. Recent, uncontrolled evidence was provided on a regimen employing four cycles of gemcitabine plus docetaxel and another that was based on four cycles of the same chemotherapy followed by four cycles of doxorubicin.[14,15] The latter regimen was associated with an interesting relapse-free survival rate compared with external controls, though the rate decreased with a longer follow-up time. A randomized trial is ongoing to compare this regimen to a no-chemotherapy arm in uterine leiomyosarcomas.

CURRENT RECOMMENDATIONS

The 2014 National Comprehensive Cancer Network (NCCN) clinical practice guidelines state that adjuvant chemotherapy for STS greater than 5 cm and intermediate to high grade in the extremities, superficial trunk, or head and neck, can be viewed as an appropriate intervention on the basis of lower-level evidence marked by limited and conflicting data.[16] Thus, adjuvant chemotherapy is a legitimate option, but is not standard. In essence, the same applies to uterine leiomyosarcomas or undifferentiated sarcomas.

The 2015 European Society for Medical Oncology (ESMO) clinical practice guidelines state that chemotherapy can be regarded as an option for patients with high-grade, deep STS that is greater than 5 cm as adjuvant or neoadjuvant treatment, but they acknowledge no consensus on its role, given the conflicting results of available studies.[17] In uterine leiomyosarcomas, the value of adjuvant chemotherapy also is said to be undetermined.

In brief, clinical practice guidelines must take into account that some evidence was provided on the potential value of adjuvant chemotherapy in STS but that this evidence is insufficient to make chemotherapy standard practice. Thus, a clinical decision shared with the patient to resort to adjuvant chemotherapy in the presence of a high risk of relapse is fully justified according to current consensus recommendations, provided that the patient is aware that it is not standard treatment.

ISSUES

Available studies mainly refer to the most typical presentations, that is, limb and superficial trunk STS. Their results are conflicting, and uncertainty has not been settled, but at least they can help by providing direct evidence. In clinical practice, one may be challenged by patients with STS who fall outside the average STS patient. In general, the primary site can be regarded as a minor source of discrepancy for the efficacy of systemic therapy, because there is no major reason, ultimately, why the same histology should benefit differently depending on the primary site. Sometimes, an atypical site entails an additional risk of relapse. For example, a pleural synovial sarcoma is likely to entail a higher risk than a limb synovial sarcoma because of the additional locoregional risk of pleural spread. Thus, one may estimate that an additional reason for selecting adjuvant chemotherapy is in place. It goes without saying that the reverse may be true as well; that is, the additional risk is even less likely to be covered by available adjuvant treatments.

Some rare histologies may pose further uncertainty, because their behavior may be less known and, most important, their chemotherapy sensitivity may deviate from that of average STS. Indeed, some histologies (e.g., epithelioid sarcoma, or alveolar soft part sarcoma) are less sensitive to standard chemotherapy for STS, and this may be a good reason to refrain from using adjuvant chemotherapy for them, when the lack of any tumor lesion prevents one from the opportunity to check tumor response (i.e., tumor sensitivity). In these cases, delaying chemotherapy to the time of relapse may be a reasonable choice, though the pursued effect of chemotherapy as an adjuvant would be different by definition. Sometimes, these histologies are less sensitive to anthracyclines plus ifosfamide but may be sensitive to other agents (e.g., leiomyosarcoma is less sensitive to ifosfamide and more sensitive to dacarbazine). In these cases, one may try to personalize the choice of the medical therapy. Of course, this adds to the uncertainty of adjuvant chemotherapy in STS, and the patient needs to be informed accordingly within a deeply shared decision-making process. In general, because the approach to the medical therapy of STS is increasingly histology driven, the assessment of whether an histology-driven approach to the adjuvant therapy of STS may improve its effectiveness is a priority for clinical research. However, when single histologies are considered, the number of eligible patients for clinical studies further diminishes, and conventional statistics faces major challenges.

With regard to the regimen choice in the adjuvant setting, aside from the possible role of histology-driven options, full-dose anthracycline-plus-ifosfamide combinations should be regarded as standard. Certainly, this conclusion may be challenged by the unclear superiority of the combination of these two drugs over single-agent doxorubicin in advanced disease, as recently suggested by a randomized trial.[18] How-

ever, this trial showed a clear superiority of the combination in terms of antitumor activity (response rate and progression-free survival). Thus, it is logical to resort to most active regimens in the adjuvant setting, aside from their superiority in terms of survival in the setting of advanced disease. Therefore, if the decision is made to use adjuvant chemotherapy in the single patient, in the absence of a personalized choice in favor of an histology-driven regimen, a full-dose combination of an anthracycline and ifosfamide can be regarded as the most logical selection today. In many institutions, this means doses of doxorubicin in the range of 60 to 75 mg/m^2, or equivalents, plus ifosfamide in the range of 6,000 to 7,500 mg/m^2.

CONCLUSION

The rarity and the heterogeneity of STS have been formidable obstacles to generating reliable evidence in favor of or against adjuvant and neoadjuvant chemotherapy. Available data are consistent with a limited degree of effectiveness, but a lack of benefit cannot be ruled out. In fact, several institutions worldwide propose systemic therapy to selected patients with STS in a shared decision-making process in conditions of uncertainty.

Eligible patients are those with a high risk of relapse, which largely is dictated by the malignancy grade and the clinical presentation. There are some rare histologies that are poorly sensitive to chemotherapy: in patients who have these histologies, adjuvant chemotherapy usually is not proposed, even when the risk would be high enough to justify adjuvant treatment, if available.

There is some evidence that systemic therapy may be placed before or after surgery with similar results, with the obvious advantage for preoperative chemotherapy to exert a local effect, which sometimes may be beneficial for the qual-ity of surgical margins. Chemotherapy may be combined with radiation therapy preoperatively so that the local effect is maximized. Evidence provided by one randomized trial would support a short course of three cycles of chemotherapy, which clearly is more acceptable for decision making in a setting of so much uncertainty over its efficacy.

Overall, chemotherapy has a limited antitumor activity in STS. Although this explains the difficulty in finding any major effect of adjuvant chemotherapy, it is clear that systemic therapy is undergoing improvements in STS. A major way forward seems to lie in histology-driven approaches. Thus, an ongoing, randomized trial is comparing three cycles of full-dose epirubicin plus ifosfamide with three cycles of an histology-driven chemotherapy regimen (i.e., gemcitabine plus dacarbazine in leiomyosarcoma; trabectedin in myxoid liposarcoma; high-dose continuous-infusion ifosfamide in synovial sarcoma; ifosfamide plus etoposide in malignant peripheral nerve sheath tumors; gemcitabine plus docetaxel in pleomorphic sarcomas). Likewise, an above-mentioned randomized trial that is ongoing in uterine leiomyosarcoma is histology-driven. In principle, molecularly targeted agents shown to be active in STS might be tested in the adjuvant setting, though they face all of the limitations that targeted therapy may encounter in solid tumors when used as an adjuvant, as demonstrated with gastrointestinal stromal tumors.[19,20]

Thus, there is room to test the effectiveness of more variegated medical therapies in the adjuvant treatment of STS, but standard practice continues to face a high degree of uncertainty. All the rules of rational decision making in conditions of uncertainty should be exploited while we look forward to the implementation of new methods for clinical studies in rare cancers.[21]

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Adjuvant Radiation for Soft Tissue Sarcomas

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OVERVIEW

Over recent decades, limb-preservation surgery in combination with radiotherapy achieves local control rates exceeding 90% for extremity soft tissue sarcoma (STS). Local control is not as successful for retroperitoneal sarcoma (approximately 60%) despite aggressive surgical approaches including en bloc resection of uninvolved adjacent organs combined with intensity modulated radiotherapy (IMRT). This review will discuss the indications for adjuvant radiation therapy (RT) for primary presentation of soft tissue sarcoma: "What," referring to the type and manner of planning and delivery of RT; "When," referring to the timing and scheduling of RT; and "Why," referring to the rationale for the use of RT will be addressed. From a practical stand point, this Educational Chapter on "adjuvant RT" will focus on pre- and postoperative RT in the context of gross total resection for extremity and retroperitoneal soft tissue sarcoma, the two most frequent paradigms for the use of adjuvant RT.

Various types of RT can be used in the treatment of STS and require attention to the application of appropriate principles for their implementation. Especially important are issues surrounding the choice of target volumes, the treatment of normal anatomy termed "organs at risk," and processes to ensure reliability in treatment delivery. Most experience in adjuvant RT of STS is based on external beam radiotherapy (EBRT). Nevertheless, other modalities exist including brachytherapy, intraoperative RT, and hadrons (i.e., protons and carbon ions).

TYPES AND METHODS OF RADIOTHERAPY DELIVERY: THE "WHAT" COMPONENT
Intensity Modulated Radiotherapy

Target coverage and protection of normal tissues appear to be superior for IMRT compared with traditional techniques in extremity STS (ESTS).[1,2] A recent retrospective review spanning noncoincident treatment time periods compared surgery combined with either IMRT (165 patients) or conventional EBRT (154 patients). Allowing for known limitations associated with studies involving treatments deployed over different eras, IMRT demonstrated significantly reduced local recurrence (LR) for primary ESTS (7.6% LR for IMRT vs. 15.1% LR for conventional RT; p = 0.02).[3]

Two recently completed prospective phase II trials, from Princess Margaret (NCT00188175) and the Radiation Therapy Oncology Group (RTOG 0630; NCT00589121), investigated if preoperative image-guided radiotherapy (IGRT) using conformal RT/IMRT can reduce RT related morbidities. The characteristics of the Princess Margaret Hospital (PMH) and RTOG 0630 trials are not identical in several ways and are contrasted (Table 1).[4,5]

The PMH trial showed less wound healing complication rates (30.5%) in lower extremity compared with the 43% risk in the previous Canadian Sarcoma Group NCIC SR2 trial that only used two-dimensional and three-dimensional RT.[6] The need for tissue transfer, RT chronic morbidities, and subsequent secondary operations for wound complications was reduced while maintaining good function and local control (93.2%). The recently published results of the RTOG-0630 trial reported a significant reduction of late toxicities compared with the NCIC-SR2 trial (10.5% vs. 37% in SR2), which is very similar to the IGRT PMH trial. Importantly, both trials defined the clinical target volume (CTV) differently (longitudinal margin of 3 cm from the gross tumor for high-grade lesions and 2 cm for low-grade lesions vs. 4 cm longitudinal margins in the PMH trial). Potentially, the reduction in CTV margins of this degree could explain the improvement in limb function with comparable local control, although, an alternative possibility is the reduction in normal tissues receiving the target dose in all dimensions that is shared by both studies.

Brachytherapy

Brachytherapy has several theoretical advantages. With appropriate selection, local dose intensification to target structures with surrounding normal tissue protection is feasible. The treatment time is shorter, theoretically limiting tumor

TABLE 1. Difference between Two Prospective IMRT Trials for Extremity Soft Tissue Sarcoma

Characteristic	RTOG 0630[4]	PMH[5]
Technique	3D conformal or IMRT	IMRT alone
Anatomic Site	Upper and lower extremity	Lower extremity only
Chemotherapy	Cohort A received induction chemotherapy plus RT (50 Gy) and concurrent chemotherapy wiht RT (44 Gy). Cohort B did not receive chemotherapy.	No chemotherapy
Postoperative Boost- R2 Surgical Margins	EBRT or BRT (LDR, HDR, IORT)	No postoperative boost
Primary End Point	Reduction of late morbidity at 2 years by RTOG/EORTC criteria ($\geq$ grade 2 lymphedema, subcutaneous fibrosis, joint stiffness)	Reduction of wound complications by the NCIC SR2 criteria at 120 days
Secondary Endpoints	Similar between both studies	Similar between both studies
Target Definitions	CTV: 3 cm longitudinal; 1.5 cm radial for high-grade lesions,	CTV: 4 cm longitudinal; 1.5 cm radial
	2 cm longitudinal; 1.0 cm radial for low-grade lesions	Surgical resection site contoured as an avoidance organ

Abbreviations: IGRT, image guided radiotherapy; RTOG, Radiation Therapy Oncology Group; PMH, Princess Margaret Hospital; 3D, 3-dimensional; IMRT, intensity modulated radiotherapy; RT, radiotherapy; EBRT, external beam radiotherapy; BRT, brachytherapy; LDR, low dose rate; HDR, high dose rate; IORT, intraoperative radiotherapy; EORTC, European Organisation for Research and Treatment of Cancer; CTV, clinical target volume; NCIC SR2, National Cancer Institute of Canada SR2 trial.

cell repopulation. Moreover, brachytherapy permits radiation volumes to be mapped according to intraoperative findings. The American Brachytherapy Society Guidelines differ from those for EBRT and also advise that brachytherapy as a sole treatment modality is contraindicated in the following situations: (1) the CTV cannot be adequately encompassed by the implant geometry, (2) the proximity of critical anatomy, such as neurovascular structures, is anticipated to interfere with meaningful dose administration, (3) the surgical resection margins are positive, and (4) there is skin involved by tumor.

> ## KEY POINTS
>
> · Trials investigating adjuvant radiotherapy for extremity soft tissue sarcoma have demonstrated a substantial benefit in local disease control for high-grade, deep seated, large tumors with control in excess of 90%.
> · A paucity of clinical trial evidence for retroperitoneal sarcoma is available. The preoperative radiotherapy approach is associated with favorable local control and overall survival with low treatment related toxicity rates.
> · Pre- and postoperative radiotherapy prospective trials questioning historic clinical target volume concepts have been completed and results are anticipated.
> · Toxicity profiles associated with the timing of radiotherapy must be considered for the individual patient and in the decision algorithm for the different approaches and types of adjuvant radiotherapy, including brachytherapy, external beam, intraoperative radiation therapy, and particle treatment.
> · Emerging evidence from prospective intensity-modulated radiation therapy trials and retrospective series demonstrate comparable local disease control with reduced acute and late morbidities including wound complication rates, limb edema, fibrosis, joint stiffness, and bone fracture incidence.

A randomized trial of 164 patients reported from Memorial Sloan Kettering Cancer Center evaluated adjuvant brachytherapy versus surgery alone and showed 10-year actuarial local control rates of 81% in the brachytherapy group and 67% in the nonbrachytherapy group (p = 0.03).[7] This improvement in local control was limited to histologically high-grade tumors without effect on low-grade lesions, which remains a matter of conjecture and uncertainty. Brachytherapy also seems less useful where implant geometry is not optimal, such as in the upper extremity or more proximal limb regions.[8] In addition, brachytherapy has been compared retrospectively with IMRT in 134 high-grade early STS[9] with similar adverse features. The 5-year local control rate was 92% for IMRT compared with 81% for brachytherapy (p = 0.04). Unfortunately, although the results of brachytherapy, including its more restrictive criteria for use, suggest lower efficacy compared with EBRT, there is no randomized, controlled trial comparing these seemingly effective local adjuvants.

Traditional brachytherapy studies, including those mentioned above, used low-dose rate techniques. High dose-rate brachytherapy has potential logistic advantages including lower radiation staff exposure, outpatient delivery, and optimized dose distributions by varying dwell times. However, wound healing complications may occur in sarcoma management and caution is also recommended when placing catheters adjacent to neurovascular structures. As yet, no large series evaluating high-dose rate brachytherapy for STS is available, nor has it been directly compared with low-dose rate, partly because of technical differences.

Particle Therapy
Emerging approaches using hadrons have putative efficacy advantages over conventional photon therapy because of their physical and radiobiologic properties. However, their

use has generally been restricted to the management of bone tumors, pediatric sarcomas, and especially skull-base and spinal lesions. Protons, intensity-modulated, and/or intraoperative electron RT targeting areas of anatomic attachment in retroperitoneal sarcoma combined with aggressive anterior surgical resection has been reported and may minimize radiation-related morbidity and reduce local recurrence, especially in patients with primary disease.[10] Further progress is awaited included the use of hadron therapies in other sarcoma sites.

Altered Fractionation

Altered fractionation can deliver doses in a shorter time period, often using higher than normal doses per fraction, or smaller than usual dose fractions more than once daily as a protracted course.

Preoperative hypofractionated RT for extremity and trunk wall STS was recently evaluated in a series of 272 patients. RT was delivered preoperatively for five consecutive days in 5 Gy per fraction. The local recurrence rate was higher (19.1%) with the hypofractionated schedule compared with many contemporary series.[11] Longer follow-up of this novel strategy is warranted.

A contrasting strategy used twice daily 1.2 Gy fractions to a total dose of 50.4 Gy in predominantly high-grade, large tumors, to exploit smaller dose per fractions in mitigating local toxicity.[12] The local control rate was 91%, with a wound complication rate of 16%, and bone fracture rate of 7.7% in an era (1978 to 1987) before IMRT or conformal techniques.

Neither hyperfractionation nor hypofractionation are likely to replace conventional daily fractionation in the short term for a combination of reasons that include the small nonrandomized nature of studies, resources needed for some protocols, concerns about efficacy and toxicity, and the fact that modern targeting techniques with IMRT may offset some of the potential benefits that underpin the choice of altered fractionation protocols.

Intraoperative Radiotherapy

Intraoperative radiotherapy (IORT) or intraoperative electron radiotherapy (IOERT) refer to the delivery of RT, including electrons, to a targeted region while the area is exposed during surgery. Most experience has been in combination with fractionated EBRT. A small subgroup (34 patients) analysis of a prospective phase II trial of IOERT, etoposide, ifosfamide and doxorubicin, and postoperative EBRT in high-grade extremity STS suggested excellent local control and overall survival (97% and 79%),[13] though superiority to large series receiving conventional EBRT is not obvious.

Interest in IORT originated in retroperitoneal sarcomas (RPS) as a result of its challenging anatomic nature. As discussed later (see Rationale for the Use of RT), an early report was a randomized trial at the National Cancer Institute that used postoperative EBRT.[14] Later the strategy evolved to combinations with preoperative EBRT as a result of toxicity imperatives. The Massachusetts General Hospital reported the long-term results of IOERT following preoperative external beam therapy (median dose of 45 Gy) and gross total resection for RPS in a selected subgroup (16 patients) receiving 10 Gy to 20 Gy of IOERT (83% local control and 74% OS) compared with no IOERT (61% local control and 30% OS). Complications in four patients included hydronephrosis, neuropathy, vaginal fistula, and uretero-arterial fistula.[15] Notably, a small number of patients were excluded because of tumor progression (two patients), partial resection (four patients), or for unresectable disease secondary to sarcomatosis (two patients). This underscores the need for prospective trials with intention-to-treat, and preferably addressing questions through randomization. The Mayo Clinic used a similar approach and also considered local control to be improved.[16] These studies were not randomized, and potentially more favorable lesions may have been chosen for IORT so that its true contribution remains unclear. In addition, although early interest appeared to focus on the potential contribution of IORT, they were also characterized by the use of preoperative EBRT which may have contributed at least as much as IORT to the apparently favorable results compared with historic series. Moreover, the likely contribution of improved surgical approaches and imaging techniques in guiding decisions and treatment may also have contributed to apparently improved outcomes. Like the efficacy results, the early toxicity results were also difficult to interpret when trying to unravel separate effects of IORT compared with preoperative RT in these retrospective series. Eventually, prospective trials discussed later (see Timing and Scheduling of Radiotherapy) became available with evidence that preoperative EBRT alone is very well tolerated acutely and led to the development of an important ongoing randomized trial (STRASS; NCT01344018) addressing the efficacy issue by comparing preoperative EBRT against surgery alone in RPS (see later discussion in Rationale for the Use of RT).

METHOD OF DELIVERY
RT Dose and Volume Definition

The most traditional method of delivering adjuvant RT is postoperatively. Guidelines have been published on how to address the technical design of the radiation volumes.[17]

Traditionally, the surgical bed is irradiated to a dose of 45 to 50.4 Gy in 1.8 to 2.0 Gy once daily fractions followed by a smaller boost volume to the tumor bed (phase II). For the latter, typically doses of 10 to 16 Gy are subsequently applied, resulting in a total dose of 60 to 66 Gy. The surgical bed is expanded with a 1.5-cm radial margin and a 4-cm craniocaudal margin to encompass microscopic disease in the surrounding tissues; the boost is applied to the original sarcoma localization with a 1.5-cm radial margin and a 2-cm craniocaudal margin (Figs. 1 and 2).

FIGURE 1. Schematic Descriptions of Target Definitions for Postoperative RT
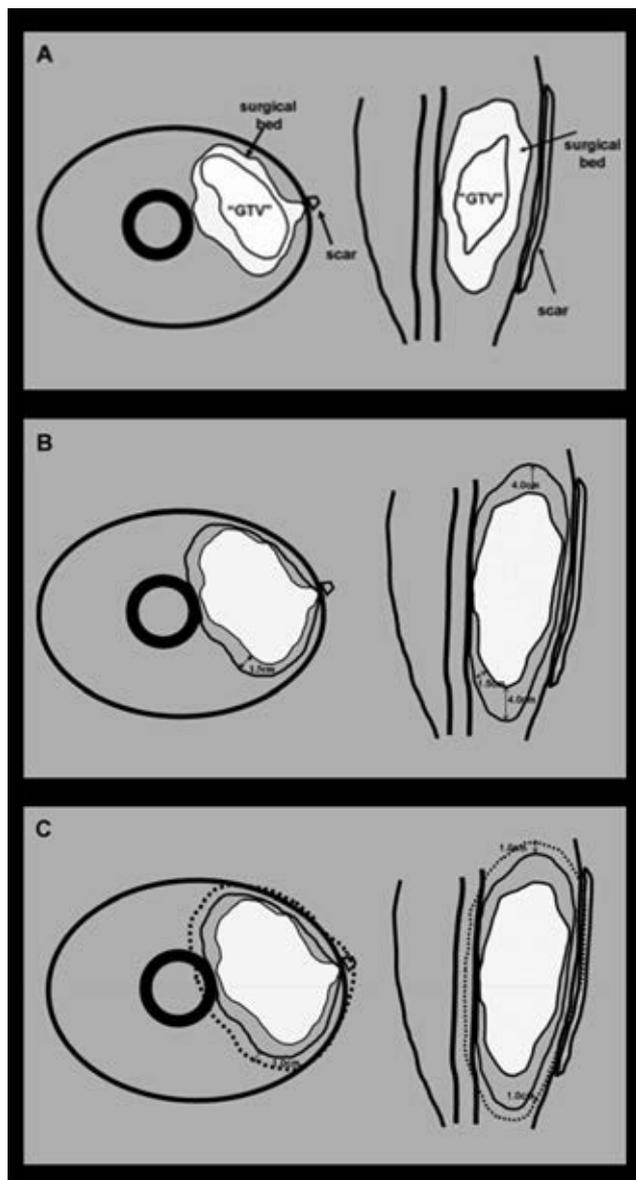
(A) Patient to receive postoperative RT. Both original sarcoma extensions (gross tumor volume [GTV]) visualized, as well as surrounding surgical bed. (B) Margins for postoperative RT elective clinical target volume (CTV) are shown; these margins were 1.5 cm in transverse plane onto, but constrained at, surfaces of bones and fascia, unless involved with tumor at surgery. Note, elective CTV remains inside the skin. Furthermore, the elective CTV is longer than the marker of the skin scar. If 4 cm expansion of reconstructed surgical volume in longitudinal direction is shorter than surgical scar, elective CTV will need to be expanded to include the surgical scar. (C) Expansion of 1 cm in all directions to produce postoperative elective planning target volume (PTV), although PTV can vary by local institutional protocols, as described in text.

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In preoperative RT, historically more recent but potentially the most prevalent approach used today, the gross tumor (GTV) is treated to a dose of 50 Gy in 25 fractions over 5 weeks with surgery following 4 to 6 weeks later. In general, the clinical target volume (CTV) encompasses the GTV with a 4-cm cranio-caudal and a 1.5-cm to 2.0-cm radial margin for microscopic disease coverage (Fig. 3). CTV should also

FIGURE 2. Schematic Descriptions of Target Definitions for Postoperative RT Boost
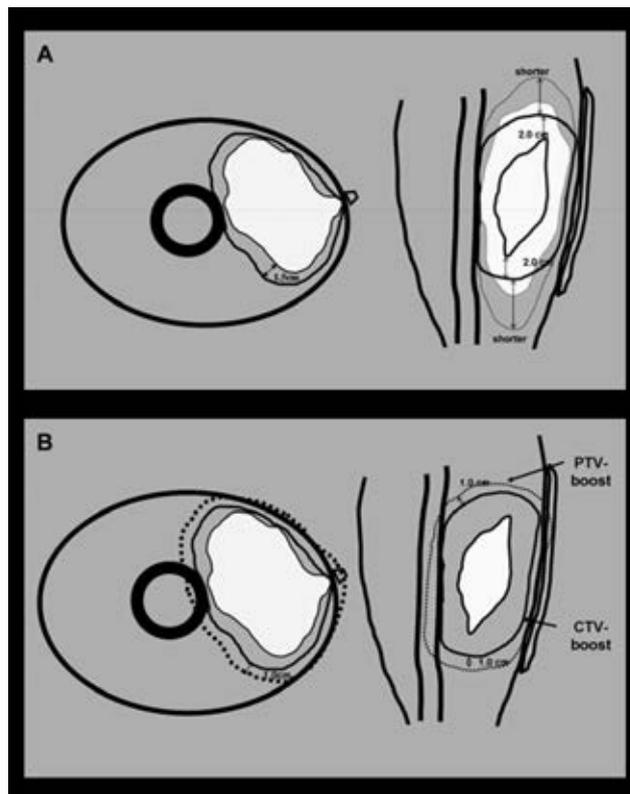
Postoperative boost clinical target volume (CTV) was the same volume as the postoperative elective CTV, except cranio-caudally. (A) In the longitudinal direction, elective CTV is 2 cm longer on both sides than the reconstructed sarcoma GTV before surgery. (B) Expansion of 1 cm in all directions of boost CTV to produce boost PTV, although PTV can vary by local institutional protocols, as described in text.

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include peritumoral edema since it may harbor tumor cells at some distance from the GTV.[18]

The defined external beam volumes for extremity STS reflect those of the prospective Canadian Sarcoma Group randomized clinical trial.[6] However, the recently completed postoperative U.K. phase III randomized VORTEX trial (NCT00423618) compared a 5-cm longitudinal margin from GTV in the standard arm to a 2-cm margin and results are awaited. The completed RTOG-0630 trial (NCT00589121) mentioned earlier defined slightly smaller preoperative RT volumes (longitudinal 3 cm), although its results may be less easily interpreted because of its nonrandomized nature. In any event, the size of the RT volume margins is not appreciably smaller than the 4-cm longitudinal margin noted above.

For RPS RT volumes, a CTV margin of 1.5 to 2.0 cm could be considered but may be reduced to protect vital radiosensitive anatomy. A typical dose of 45 to 50.4 Gy is given in 1.8 to 2.0 Gy fractions. When evaluating patients for RT planning, the functional capacity of the liver and differential function of the kidneys is paramount, as they may need to be resected or irradiated. A study that evaluated the spatial and volumetric changes of RPS during preoperative RT also as-

FIGURE 3. Schematic Descriptions of Target Definitions for Preoperative RT
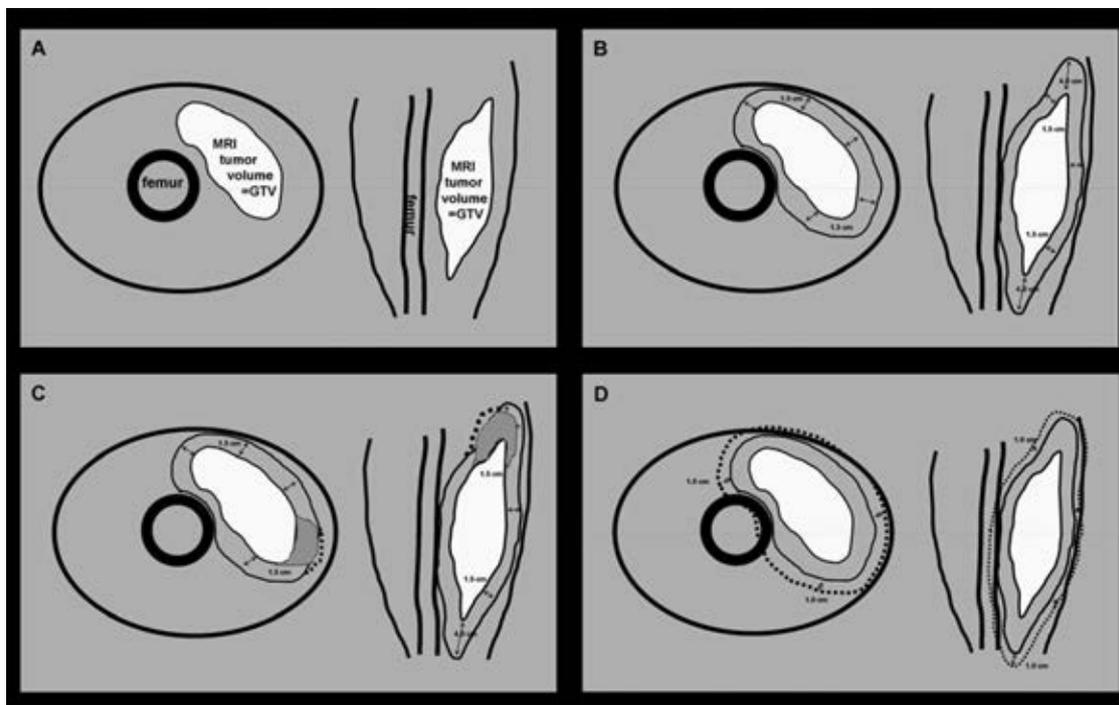
(A) Patient to be treated with preoperative RT. Sarcoma delineated using T1-weighted, postgadolinium MRI scan fused to planning CT scan. This gross tumor volume (GTV) does not include peritumoral edema, generally best seen on T2-weighted MRI scan. (B) GTV transversely expanded with 1.5 cm, but constrained at surfaces of fascia and bones, unless invaded. Longitudinally, expansion was 4 cm. Note, this was a sarcoma case without peritumoral edema. (C) Sarcoma case with peritumoral edema, with GTV also transversely expanded with 1.5 cm and constrained at surfaces of fascia and bones, unless invaded. Longitudinally, expansion was 4 cm. Note, CTV has been manually edited (bold dashed line) to encompass edema zone in both transverse and coronal planes. Peritumoral edema indicated by striped zone. (D) Delineation of final preoperative planning target volume (PTV) by expansion of CTV with 1 cm in all directions, although PTV can vary by local institutional protocols, as described in text.

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sessed target volume coverage during inter- and intrafractional breathing.[19] Four-dimensional CT simulation and planning was suggested for superiorly located tumors (GTV centroid above the L2/3 junction) to account for respiratory motion most pronounced in the superior to inferior dimension (maximum of 14 mm).

Features of RT Planning and Delivery

Techniques such as IMRT, brachytherapy, and particle therapies, or a combination of techniques (i.e., brachytherapy combined with EBRT), are able to tailor the dose distribution to avoid vulnerable normal tissue structures with superior coverage of the CTV, even where vital anatomy is juxtaposed.

In a study of 363 patients with extremity STS treated with EBRT and surgery, a dose-related fracture rate was apparent with a median of 50 months of follow-up. Radiation induced fractures were identified in 27 patients (crude fracture risk of 6.3%), 20 of whom received 60 to 66 Gy (fracture rate, 10%), and three received 50 Gy (2% risk).[20] A separate retrospective dosimetric review of bone fractures (that occurred in 21 patients) was compared with a random sample without fractures (53 patients) to determine fracture risk factors. Bone fracture risk was reduced if the volume of irradiated bone to

40 Gy or greater was less than 64%, the mean bone dose was less than 37 Gy, or the maximum dose along the bone length of bone was less than 59 Gy.[21] This study provides evidence-based dose volume bone avoidance objectives for RT planning, which was further investigated in additional patients (176 patients with lower and 54 patients with upper extremity STS) with a median follow-up of 41.2 months.[22] The overall risk of fracture was 1.7% (four out of 230 patients), which compares favorably to the previous reported incidence of 6.3%, and suggests that efforts to achieve bone avoidance are meritorious.

Quality Assurance of Dosimetry

In addition to employing evidence-based dose volume objectives for optimal RT planning, preoperative RT also requires additional considerations. As previously discussed (see RT Dose and Volume Definition), volumetric changes occur during preoperative RT in RPS suggesting that imaged-guided tracking of GTV size and position may improve preoperative RT quality and prompt replanning.[19] Similarly, volume changes in extremity STS occur during preoperative RT[23] and adaptive RT may need to account for these changes. A 1 cm tumor volume change on imaging is a reliable threshold to identify potential GTV underdosage for increasing tumor volumes during extremity

STS IMRT, indicating the need for reliable on-board imaging to detect target volume changes.[24]

TIMING AND SCHEDULING OF RADIOTHERAPY: THE "WHEN" COMPONENT

The two most common methods of EBRT delivery are preoperatively or postoperatively. Postoperative delivery is associated with increased limb fibrosis, edema, joint stiffness, and bone fractures. Preoperative RT results in an increased rate of acute wound complications.[6]

Several studies have reported the late morbidities following pre- and postoperative RT in extremity STS. Long-term follow-up of patients treated in the Canadian Sarcoma Group NCIC trial (SR2) showed that, of 129 patients evaluable for late toxicity, 48.2% in the postoperative group compared with 31.5% in the preoperative group had grade 2 or greater fibrosis (p = 0.07).[25] Edema was more frequently seen in the postoperative group (23.2% vs. 15.5%), as was joint stiffness (23.2% vs. 17.8%). Patients with these complications had lower function scores (all p values < 0.01) on the Toronto Extremity Salvage Score and the Musculoskeletal Tumor Society Rating Scale. Field size predicted greater rates of fibrosis (p = 0.002) and joint stiffness (p = 0.006), and marginally predicted edema (p = 0.06). Acute wound healing complications were twice as common with preoperative compared with postoperative RT. The increased risk was almost entirely confined to the lower extremity (43% associated with preoperative vs. 21% with postoperative timing; p = 0.01).

The influence of time interval between preoperative EBRT and surgery on the development of wound complications in extremity sarcoma has been studied. Although the interval had little influence, the data still suggest that the optimal interval to reduce potential wound complications was 4 or 5 weeks between RT and surgery.[26]

Although toxicity is a known accompaniment of the combination of EBRT and surgery, these problems and considerations do not preclude the use of RT in the management of ESTS. In fact, the gain in local control is at least as large as the benefit of adjuvant RT in breast conserving therapy for invasive breast cancers.[27] Furthermore, for high-grade sarcomas, a survival benefit has been suggested.[28]

Whether a radiation therapy boost is needed following preoperative RT and surgery with positive resection margins has been questioned in a retrospective review of 216 patients with ESTS; 52 received preoperative RT (50 Gy) alone and were compared with 41 who received preoperative RT with a postoperative boost (generally 16 Gy). A portion of the population did not receive radiotherapy at all, or received post-operative RT and were excluded (123 of 216 patients). Patients who received the postoperative boost had lower 5-year local recurrence-free rates (73.8% vs. 90.4% for preoperative RT only), indicating that the postoperative boost provides no obvious advantage.[29] A similar study of 67 patients yielded almost identical results.[30] These results suggest that a benefit from a delayed postoperative boost following preoperative RT and surgery is at best debatable, and the increased risk and challenges of managing later RT morbidity (e.g., radiation-induced fractures) resulting from the higher radiation doses involved should be considered.

Finally, preoperative EBRT may be particularly suited to the management of RPS. Its potential role was mentioned briefly in the discussion of IORT because of the way these approaches evolved. Radiotherapy delivered to an in situ tumor has the advantages of treating a well-defined and undisturbed tumor volume where the tumor also acts as a tissue-expander to displace small bowel and other radio-sensitive viscera from the radiation volume. Preoperative external beam radiotherapy for RPS was associated with minimal acute toxicity in two prospective clinical trials from the Princess Margaret Hospital and The University of Texas MD Anderson Cancer Center[31,32] with no increase in wound healing complications. Long-term follow-up of both trials combined indicated that preoperative radiotherapy may be associated with favorable local control and overall survival.[33] This has been further addressed in the very long-term follow-up of the PMH study.[34]

The minimal early toxicity reports of preoperative EBRT were further confirmed in an additional trial where only one of 20 patients experienced gastrointestinal toxicity of grade 2 or greater and one additional patient experienced leucopenia during the EBRT phase.[35] Additional toxicity manifesting later[35,36] included a 33% severe postoperative complication rate and may relate to the subsequent IORT phase. This underlines the importance of prospective data collection in addressing complex toxicity reporting from sequential phases of adjuvant local therapy that is difficult to interpret in retrospective studies such as those reported earlier from the Mayo Clinic and MGH.[15,16] In such retrospective studies where toxicity is reported remotely (often years later), only aggregated toxicities can realistically be reported, since differential toxicities from separate treatments are generally neither defined nor attributed distinctly at the time of occurrence.

RATIONALE FOR THE USE OF RT: THE "WHY" COMPONENT
Adjuvant Radiotherapy

Even in large, deep seated, intermediate- to high-grade sarcomas, the combination of limb sparing surgery with RT permits more conservative surgical resections and results in high local control results of approximately 90%.[6,17] The gain should be balanced against the costs. The scope of this domain is broad and includes RT treatment planning and delivery, patient expenses including travel and work leave, and the cost to health care when managing acute and late radiation-induced morbidities.

To fully appreciate the role of RT in STS, it is also informative to reflect on the outcome in randomized trials of patients in whom RT was either not applied or was of only moderate

dose intensity for the given circumstance (e.g., the RPS setting for the Sindelar trial outlined later).

Rosenberg et al randomly assigned patients to either receive an amputation (16 patients) or limb-sparing surgery plus adjuvant RT (27 patients). There were no local recurrences in the amputation group, but four in the limb-sparing group (local control 85% vs. 100%, p = 0.06), with no difference in overall survival.[37]

Two subsequent trials compared conservative surgery alone with similar surgery combined with adjuvant RT in predominantly ESTS. The first study was discussed earlier, and patients were randomly assigned to receive adjuvant brachytherapy or surgery alone (see Types and Method of RT Delivery, Brachytherapy).[7]

Yang et al at the NCI randomly assigned 141 patients to receive postoperative RT or not. They reported that high-grade lesions (present in 91 patients) benefited from adjuvant EBRT (10-year local control rates of 78% vs. 100%; p = 0.03) as did low-grade sarcomas (present in 50 patients; 10-year local control rates of 68% vs. 95%; p = 0.067).[38] The gain in local control by the addition of RT resulted in a substantial and persistent reduction in joint motion. The earlier data was recently confirmed with a median follow-up of 17.9 years.[39]

The high risk of local failure following surgery has made adjuvant RT an attractive option for RPS, but its role remains controversial and there is a paucity of trials available. At the National Cancer Institute, Sindelar et al reported the prospective, randomized trial discussed earlier (see Intraoperative Radiotherapy). In the study, 35 patients with surgically resected RPS were randomly assigned to receive postoperative EBRT (50 to 55 Gy) versus postoperative EBRT (35 to 40 Gy) and IORT (20 Gy). The median follow-up was 8 years. Locoregional recurrence was substantially lower with IORT (40% vs. 80% with external beam alone), but with high toxicity and no survival difference. However, only modest EBRT doses (35 to 40 Gy) delivered postoperatively without IORT resulted in very high recurrence rates.

Withholding Adjuvant Radiotherapy

Although the benefit of adjuvant RT is apparent in phase III trials, guidelines and several published series also recommend withholding RT in subsets of patients. Patients with early-stage disease, including small size, superficial location, and/or low-grade histologic subtypes are candidates. The caveat underpinning the decision is that a resection should be undertaken with oncologically appropriate margins and/or intact fascial planes.[40] Such favorable presentations do not eliminate local recurrences after surgery alone, but the risk is low. For example, in the randomized study from Yang et al, six of 19 low-grade cases experienced local recurrence without RT versus one of 22 with RT (p = 0.067), but other anatomic factors (size and depth) also influence outcome.[38,39] In two other series in which patients were selected not to receive RT based on small size, favorable histology of extremity/trunk STS, and wide margin resections, the

10-year local recurrence rate was 7% to 16.2% for the entire group, and 0% to 10.6% for the subgroup after R0 surgery.[41,42] Nevertheless, recurring cases did not fare worse with respect to disease specific- and overall survival compared with similar patients without local disease recurrence. The decision algorithm includes factors that address the ability to salvage recurrence and the likelihood that metastasis will not develop. Morbidity as a result of recurrent disease management is an additional concern and not readily accounted for.

A published nomogram based on 684 patient clinico-pathologic factors estimated the risk of local recurrence after limb-sparing surgery without postoperative RT.[43] For example, a patient younger than age 50, with a smaller than 5 cm high-grade extremity pleomorphic malignant fibrous histiocytoma resected with negative margins, would have a 3-year local recurrence rate of less than 10%. This patient could undergo surgery alone if the tumor location permits potential limb salvage surgery in the event of subsequent local recurrence. Despite the inherent bias in a retrospective review of this nature, this nomogram shows promise as a clinical tool for assessing the risk of local recurrence and the need for adjuvant therapy with specific attention to whether RT can be omitted.

In the management of RPS, the role of adjuvant RT is much less clearly defined as compared to the treatment of ESTS. A number of large institutional studies[44,45] provide superior results with modern and/or more aggressive surgery alone than were obtained historically, thereby questioning the contribution of RT in this setting. Based upon these considerations, the European Organisation for Research and Treatment of Cancer (EORTC) is currently conducting a phase III, randomized study of preoperative RT plus surgery versus surgery alone for patients with RPS (STRASS Trial; NCT01344018).[46] This is a multi-institutional trial addressing preoperative RT specifically compared with surgery only. We await the results of this important and well-accruing trial that has shown a 54% global recruitment to date and is on target for completion.[46]

CONCLUSION

The local recurrence of ESTS following limb-sparing surgery alone is in the range of 30% to 50%. In contemporary series employing highly conformal RT including IMRT, the addition of pre- or postoperative RT improves local control to approximately 90% or greater with excellent functional outcome. For RPS, the benefit of RT has not yet been proven, but if considered, preoperative RT seems to be the safest process of delivery. An ongoing multi-institutional randomized trial should confirm its role. As experience evolves, including a better understanding of pathology and underlying molecular disease characteristics, as well as imaging modalities, additional strategies should further improve the therapeutic ratio following RT for local control of STS in all anatomic sites.

Disclosures of Potential Conflicts of Interest

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Latest Advances in Systemic Therapy for Bone Sarcomas

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Systemic Therapy for Osteosarcoma and Ewing Sarcoma

Paul A. Meyers, MD

OVERVIEW

Curative therapy for both osteosarcoma and Ewing sarcoma requires the combination of effective systemic therapy and local control of all macroscopic tumors. Systemic therapy for osteosarcoma consists of multiagent chemotherapy. The most common regimen uses cisplatin, doxorubicin, and high-dose methotrexate. Addition of ifosfamide and etoposide to treatment for patients with poor initial response to therapy does not improve outcome. Addition of interferon to treatment for patients with favorable initial response does not improve outcome. Addition of liposomal muramyl tripeptide to chemotherapy may improve overall survival. Systemic therapy for Ewing sarcoma consists of multiagent chemotherapy including doxorubicin, vincristine, etoposide, and cyclophosphamide and/or ifosfamide. Increased dose intensity of therapy, either by shortening the intervals between cycles of chemotherapy or by increasing doses of chemotherapy, improves outcome. Regimens such as irinotecan/temozolomide or cyclophosphamide/topotecan have shown activity in metastatic recurrent Ewing sarcoma. Trials are ongoing to evaluate the addition of these drugs to existing multiagent regimens in order to test their ability to improve outcome. High-dose systemic therapy with autologous stem cell reconstitution is being tested for patients at high risk for recurrence; definitive results await completion of a prospective randomized trial.

Osteosarcoma and Ewing sarcoma are the two most common primary tumors of the bone seen in children, adolescents, and young adults. Both diseases almost always present with systemic metastasis and attempting to cure them by local measures alone is very unlikely. Successful treatment for both diseases requires the combination of effective systemic therapy and local measures directed at all sites of clinically detectable disease. Substantial progress has been made in the cure rate of these primary bone sarcomas when they present without clinically detectable metastatic disease. Curing patients who present with metastasis is much less likely.

OSTEOSARCOMA

Before the introduction of systemic therapy, cure rates for osteosarcoma were less than 20%, even among patients who presented without clinically detectable metastatic disease.[1] The introduction of multiagent chemotherapy improved the probability for cure to 60% to 70%.[1] There are only four chemotherapy agents with evidence of objective responses in osteosarcoma.[2] Anninga et al summarized the results of single-agent phase II trials of these agents in osteosarcoma, as shown in Table 1.

The reported objective response rates are probably an underestimate of true response, as osteosarcoma tumors can exhibit substantial necrosis following chemotherapy without change in size because of the osteoid matrix produced by the tumor.

Various combinations of the four active agents have been employed in clinical trials for the treatment of osteo-sarcoma—some with the addition of etoposide. Anninga et al summarized all published cohorts of patients with osteosarcoma.[2] Any trial that employed three of the active agents had a better outcome than any trial that employed only two. Trials that used all four active agents did not have outcomes superior to trials that employed any three.

When osteosarcoma is treated before definitive surgery, necrosis in the primary tumor can be assessed at the time of definitive surgical resection and strongly correlates with subsequent event-free survival (EFS) and overall survival.[3] Less necrosis in the primary tumor is associated with a higher probability of recurrence and death. Many trials have employed the strategy of tailoring: altering chemotherapy following definitive surgery to intensify therapy for patients with less necrosis following initial chemotherapy. The European and American Osteosarcoma Study Group (EURAMOS) performed the definitive prospective randomized trial to test the strategy of tailoring therapy.[4] All patients received initial therapy with cisplatin, doxorubicin, and high-dose methotrexate (MAP). Necrosis was assessed in the definitive surgical resection after 10 weeks of initial therapy. Patients with favorable necrosis were randomly selected to receive continuation of MAP and MAP with the addition of interferon-alfa. Patients with less necrosis were randomly selected to receive either continuation of MAP or MAP with the addition of high-dose ifosfamide and etoposide. Chemotherapy with MAP continued for 20 weeks following definitive surgery. The addition of interferon to MAP did not improve the prob-

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TABLE 1. Single-Agent Chemotherapy Activity in Osteosarcoma

Drug	Objective Response Rate
Doxorubicin	43%
Ifosfamide	33%
Methotrexate	32%
Cisplatin	26%

ability of EFS for patients with higher necrosis.[5] The addition of high-dose ifosfamide and etoposide to MAP did not improve the probability of EFS for patients with less necrosis.[6] The results of EURAMOS-1 suggest that MAP chemotherapy can be considered a standard approach to the treatment of osteosarcoma.

Substantial preclinical evidence suggests that bisphosphonates might be active against osteosarcoma, and a small pilot study explored the use of pamidronate in combination with MAP chemotherapy for the treatment of osteosarcoma.[7] This was a pilot trial. A larger prospective randomized trial carried out in France determined that the addition of zoledronate to chemotherapy did not improve outcome.[8] There does not appear to be a rationale for pursuing bisphosphonates as part of osteosarecoma thearpy.

Liposomal muramyl tripeptide (MTP) is a derivative of the Bacillus Calmette-Guérin cell wall, which stimulates macrophages to become tumoricidal. Clinical trials of MTP in osteosarcoma have decreased the probability of subsequent metastasis for patients with a first metastatic recurrence of osteosarcoma.[9] A prospective randomized trial of the addition of MTP to chemotherapy for the treatment of osteosarcoma demonstrated a trend toward improved EFS and a statistically significant improvement in overall survival (p = 0.03).[10] MTP is approved for use in combination with chemotherapy in the treatment of localized osteosarcoma for patients age 2 to 30 in the Europe, Mexico, Brazil, Israel, and Turkey. MTP is not approved for use in the United States.

Strategies under clinical investigation in osteosarcoma include the use of denosumab, monoclonal antibody therapy directed against the GD2 antigen, and investigational chemotherapy.

KEY POINTS

- The primary bone sarcomas of young patients require systemic therapy for cure.
- Systemic therapy for osteosarcoma can cure approximately 70% of patients who present with localized disease.
- Cure rates for osteosarcoma have not changed for over 20 years.
- Systemic therapy for Ewing sarcoma can cure approximately 70% of patients who present with localized disease.
- Increased dose intensity of therapy improves the outcome of treatment for Ewing sarcoma.

EWING SARCOMA

Before the introduction of systemic chemotherapy, Ewing sarcoma had a cure rate of less than 10%, even among patients who presented with localized disease.[11] The introduction of systemic chemotherapy improved the outcome for Ewing sarcoma. Treatment with multiagent chemotherapy will achieve long-term EFS for roughly 70% of patients who present without clinically detectable metastatic disease.[12-14] When patients present with lung metastasis, long-term EFS rates are 30% to 50%; when patients present with metastasis to distant bones or bone marrow, EFS is less than 20%.[12]

An intergroup study conducted by the Pediatric Oncology Group and the Children's Cancer Group demonstrated that the addition of ifosfamide and etoposide to cyclophosphamide, doxorubicin, and vincristine significantly improved outcomes for patients with localized Ewing sarcoma.[12] Following this study, the five-drug combination became the preferred background for treatment and for clinical trials in North America. In these trials, chemotherapy was administered as cycles of cyclophosphamide, doxorubicin, and vincristine and cycles of ifosfamide and etoposide. A single-institution study from the Memorial Sloan Kettering Cancer Center (MSKCC) reported a high rate of EFS with the use of very high-dose alkylating agent therapy given over a shorter duration (21 weeks).[15] The Children's Oncology Group (COG) performed a trial in which patients treated with the five-drug combination were randomly selected to receive conventional doses or higher doses of cyclophosphamide.[13] They reported no improvement in outcome with higher-dose cyclophosphamide, but the regimen called for higher doses of cyclophosphamide in only early cycles and did not equal the MSKCC in dose intensity over the duration of treatment. In a subsequent trial, COG studied dose intensification by shortening the interval between cycles of chemotherapy.[14] Administration of the usual five-drug combination every 2 weeks for 28 weeks achieved EFS (p = 0.048), which was statistically superior to the EFS observed with the five-drug combination administered every 3 weeks for 42 weeks. Increasing dose intensification by either increasing the dose of alkylating agents or by shortening the intervals between cycles of chemotherapy has been associated with improved outcome in the treatment of Ewing sarcoma (Table 2).

The demonstration of improved outcome with increased dose intensification for patients with localized Ewing sarcoma led to the concept that even further dose intensification of therapy might improve outcome for patients at higher risk for failure. A very dose-intensive regimen including higher doses of doxorubicin was tried with patients with Ewing sarcoma metastatic at initial presentation.[16] The regimen failed to improve EFS and was associated with a very high rate of secondary leukemia. Administration of chemotherapy in myeloablative doses followed by autologous stem cell reconstitution has been used for patients with Ewing sarcoma metastatic at initial presentation and for patients following

TABLE 2. Chemotherapy Dose Intensification: Planned Doses in mg/m^2/Week

Chemotherapy	CCG 7924[13]		AEWS 0031[14]		MSKCC P6[15]
Planned protocol duration	Standard	Intensified	Standard	Intensified	Q3 wk
	48 wk	30 wk	Q3 wk	Q2 wk	21 wk
			42 wk	28 wk	
Doxorubicin	7.8	12.5	8.9	13.4	14.3
Cyclophosphamide	225	366	200	300	800
Ifosfamide	1,500	2,400	1,500	2,250	2,000
Five-Year EFS	72%	70%	65%	73%	82%

Abbreviations: CCG, Children's Cancer Group; AEWS, Ewing sarcoma study sponsored by the Children's Oncology Group; MSKCC, Memorial Sloan Kettering Cancer Center; wk, week; EFS, event-free survival.

recurrence of Ewing sarcoma. No regimen has conclusively demonstrated benefit for this strategy, and most reports are small series that do not adequately control for selection bias. The European Ewing sarcoma consortium began a trial in 1999 in which all patients received common initial therapy. Patients with lung metastases at initial presentation or patients with poor response to initial therapy were randomly assigned to either continue conventional chemotherapy or undergo consolidation with high-dose therapy and autologous stem cell reconstitution. As of 2014, the results of this study remained blinded because the accrual goals set at study initiation had not been met.

When Ewing sarcoma recurs following initial therapy, the prognosis is extremely poor, with less than 5% of patients remaining alive more than 2 years following recurrence.[17,18] Several chemotherapy regimens have shown activity in relapsed Ewing sarcoma, including cyclophosphamide/topotecan, irinotecan/temozolomide, and gemcitabine/docetaxel.[19-21] COG is conducting a randomized trial of the addition of cyclophosphamide/topotecan to the five-drug background. MSKCC is conducting a trial of the addition of irinotecan/temozolomide to the five-drug background.

Monoclonal antibodies against the insulin-like growth factor 1 receptor (IGF1R) showed activity in recurrent Ewing sarcoma.[22] Unfortunately, most pharmaceutical companies abandoned development of these antibodies because they failed to show activity in common adult cancers, and planned prospective randomized trials of these agents for patients with newly diagnosed Ewing sarcoma could not proceed.

One manufacturer transferred supply to the National Cancer Institute (United States), which became the sponsor for a COG trial studying the addition of a monoclonal antibody against IGF1R to the five-drug background for patients with newly diagnosed Ewing sarcoma metastatic at initial presentation. This trial is ongoing.

Strategies under clinical investigation in Ewing sarcoma include the use of PARP inhibitors as single agents and in combination with chemotherapy, as well as phase I and phase II trials.

Currently available clinical trials for patients with newly diagnosed Ewing sarcoma:

- Combination Chemotherapy in Treating Patients with Nonmetastatic Extracranial Ewing Sarcoma. COG AEWS1031. (www.cancer.gov/clinicaltrials/search/results?protocolsearchid=13732535)
- Combination Chemotherapy with or without Peripheral Stem Cell Transplantation, Radiation Therapy, and/or Surgery in Treating Patients with Ewing's Sarcoma. EURO-EWING-INTERGROUP-EE99. (www.cancer.gov/clinicaltrials/search/results?protocolsearchid=13732535)
- Combination Chemotherapy with or without Ganitumab in Treating Patients with Newly Diagnosed Metastatic Ewing Sarcoma. COG AEWS1221. (www.cancer.gov/clinicaltrials/search/results?protocolsearchid=13732535)
- A Phase II Study of Irinotecan and Temozolomide in Combination with Existing High-Dose Chemotherapy for Patients Newly Diagnosed with Ewing Sarcoma. MSKCC 13–068. (www.mskcc.org/cancer-care/clinical-trials/clinical-trial?keys=Ewing+sarcoma&field_trial_diseases_value=All&phase=All)

Disclosures of Potential Conflicts of Interest

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The Biology and Management of Cartilaginous Tumors: A Role For Targeting Isocitrate Dehydrogenase

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OVERVIEW

Chondrosarcomas are rare mesenchymal neoplasms defined by the production of abnormal cartilaginous matrix. Conventional chondrosarcoma is the most common histology. The management of primary conventional chondrosarcoma generally is surgical with the possible addition of radiation therapy. Treatment of conventional chondrosarcoma is problematic in unresectable or metastatic disease because the tumors tend to be resistant to standard sarcoma chemotherapy regimens. Previous attempts at targeted therapy, including inhibitors of Hedgehog signaling, the mTOR pathway, and platelet-derived growth factor receptor (PDGFR) have been largely disappointing. However, heterozygous mutations in isocitrate dehydrogenase (*IDH*) enzymes recently have been identified in chondrogenic neoplasms, with mutations reported in approximately 87% of benign enchondromas, 70% of conventional chondrosarcomas, and 54% of dedifferentiated chondrosarcomas. The normal *IDH* protein continues to produce alpha-ketoglutarate (alpha-KG) whereas the mutant IDH protein converts KG to the oncometabolite 2-hydroxyglutarate (2-HG). Clinical trials of novel IDH inhibitors are ongoing, with evidence of early activity in *IDH*-mutant leukemias. IDH inhibitors show antitumor effects against *IDH*-mutant chondrosarcoma cell lines, supporting the inclusion of patients with chondrosarcoma with IDH mutations on IDH inhibitor clinical trials for solid tumors. Targeting *IDH* mutations may offer hope of a novel antineoplastic strategy not only for patients with chondrosarcomas, but also for other solid tumors with aberrant IDH activity.

Chondrosarcomas constitute a diverse group of neoplasms with varied morphologic features and different clinical behaviors, defined by the production of neoplastic cartilage matrix by the tumor cells.[1] Chondrosarcomas are the second most frequent primary sarcoma arising in bone after osteosarcoma,[2-5] accounting for 20% to 27% of malignant bone neoplasms.[6] They may occur at any age, but typically they are seen more frequently in older adults.[7,8] The clinical behavior is quite variable, with low-grade tumors displaying slow growth and low metastatic potential, to high-grade tumors that can be highly aggressive with the propensity for distant metastases. Because of the avascular matrix and low percentage of dividing cells, most chondrosarcomas are inherently resistant to cytotoxic chemotherapy and are relatively radiation-resistant, with the exception of the mesenchymal subtype.[7] Thus, complete surgical resection with wide margins remains the most critical component of therapy, whenever possible, for patients with primary tumors.[9] Unfortunately, many patients present with inoperable disease at the time of diagnosis or recur with metastatic disease, and more than 10% of recurrent chondrosarcomas are of a higher grade than the original tumor.[7] Current research focuses on improving our understanding of chondrosarcoma biology and identifying new therapeutic approaches, especially for patients in whom curative surgery is not indicated.[10] Our objective in this review is to discuss classification of chondrosarcomas in the setting of standard treatments, and to review novel pathways that may lead to novel therapies in the future.

CLASSIFICATION

Cartilaginous tumors are categorized based on the *WHO Classification of Tumours of Soft Tissue and Bone* (Tables 1 and 2).[11] The importance of expert pathologist review in classification of all sarcomas cannot be overemphasized. These tumors may have overlapping histologic features and often require additional immunohistologic and genetic testing for definitive diagnosis. Various studies have suggested that histologic grade, size, stage, and anatomic location of the lesion are fundamental prognostic features.[12,13] In an analysis of 2,890 patients with chondrosarcoma from the Surveillance, Epidemiology, and End Results (SEER) database, only grade and stage were identified as independent prognostic factors

TABLE 1. Benign Cartilaginous Tumors of Bone

Benign	Molecular Features	Clinical Features
Enchondroma	*IDH1* or *IDH2* mutation	Ollier's disease or Mafucci syndrome; 50% risk of syndromic transformation; pain may herald malignant transformation
Osteochondroma	*EXT1* or *EXT2* deletion or inactivating mutation	Arise in long bones around knee or elbow; risk of fracture; 5% risk of transformation to peripheral conventional chondrosarcoma
Chondroblastoma	*H3F3B* Lys36Met	Arise around the knee or proximal humerus; younger individuals; more common in men; rarely metastasizes
Chondromyxoid Fibroma	*GRM1* gene fusion usually t(1;5)(p13;p13)	Arise in metaphysis of long bones; younger individuals; very rare malignant transformation

for survival.[14] However, as detailed below, histologic subtype is very important in guiding therapy.

Benign Cartilaginous Tumors

Benign cartilaginous tumors commonly are found in children and young adults. Many have a characteristic appearance on radiology films and are not biopsied. Although most tumors can be treated conservatively, enchondromas and osteochondromas have the potential to transform into a higher-grade chondrosarcoma, particularly in the setting of an underlying *IDH* mutation as seen in Ollier's disease and Maffucci syndrome.[15-18] Details of genetic and molecular abnormalities and clinical presentation can be found in Table 1.

Conventional Chondrosarcoma of the Bone

Conventional chondrosarcomas make up approximately 85% of all chondrosarcomas (Table 2). These tumors most commonly arise in the proximal femur, bones of the pelvis, and proximal humerus.[19,20] Clinical symptoms are nonspecific. Pain is the most frequent symptom, occurring in at least 95% of patients. Pathologic fractures are found at the time of diagnosis, affecting 3% to 17% of patients.[6] Conventional chondrosarcomas are divided into three histologic catego-

ries. Central conventional chondrosarcoma (CCC) represents approximately 75% of all chondrosarcomas. These cancers arise within the medullary cavity from previously normal-appearing bone. Although most are thought to arise de novo, as many as 40% of central chondrosarcomas may arise from a preexisting benign cartilage lesion (Table 1), or enchondroma.[7,8,11,21,22] These secondary chondrosarcomas often may be lower-grade with less metastatic involvement.[23] Malignant transformation has been described in patients with Ollier's disease (enchondromatosis) and Maffucci syndrome (enchondromatosis associated with soft-tissue hemangioma).[18] Most cases of chondrosarcoma in Ollier's disease and Maffucci syndrome are linked to *IDH1* or *IDH2* mutations.[24,25] Peripheral conventional chondrosarcoma (PCC) is rarer, occurs in younger patients, and by definition arises in an osteochondroma. PCC also is a tumor that is resistant to chemotherapy and relatively resistant to radiation therapy. A third type of chondrosarcoma is periosteal chondrosarcoma (also known as juxtacortical chondrosarcoma), which arises from the external surface of bone.[26] This tumor accounts for less than 1% of all chondrosarcomas.[14] Interestingly, despite high-grade histology, this subtype has a more favorable prognosis with adequate surgical management.[14,27] It tends to affect slightly younger adults, with slow growing masses arising from long bones, particularly the posterior distal femoral metaphysis or diaphysis.[6]

The other 10 to 15% of all chondrosarcomas are infrequent subtypes, such as dedifferentiated, myxoid, clear cell, and mesenchymal chondrosarcomas.[11,28] Mesenchymal chondrosarcoma is a high-grade malignant bone tumor that is comprised of biphenotypic well-differentiated cartilaginous cells and undifferentiated high-grade small round blue cells. These occur in younger patients, arise in the axial skeleton, and have a high propensity of metastasis at the time of diagnosis. The small round blue cell component of this subtype of chondrosarcoma may respond to conventional chemotherapy regimens used for Ewing sarcoma or rhabdomyosarcoma. Therefore, accurate diagnosis of the precise subtype is critical for appropriate management and best outcomes.

Dedifferentiated Chondrosarcoma

Dedifferentiated chondrosarcoma is an uncommon but aggressive subtype of chondrosarcoma that comprises approximately 10% of all chondrosarcomas.[6,11,14] The disease tends

KEY POINTS

- Treatment recommendations for chondrosarcoma depend heavily on histologic subtype, which predicts sensitivity to chemotherapy and radiation.
- RECIST response rates to anthracycline-containing chemotherapy regimens are less than 20% for the most common conventional and dedifferentiated subtypes.
- Isocitrate dehydrogenase (IDH) enzymes normally catalyze conversion of isocitrate into alpha-ketoglutarate during the citric acid cycle, a function impaired in mutant enzymes.
- Mutated IDH enzymes also possess a unique gain-of-function phenotype that converts alpha-ketoglutarate to an oncometabolite, 2-hydroxyglutarate, not present in normal cells.
- *IDH* mutations have been identified in numerous solid and hematologic cancers, including chondrosarcomas, which have led to ongoing clinical trials of novel IDH1 and IDH2 inhibitors.

TABLE 2. Malignant Cartilaginous Tumors of Bone

Malignant	Molecular Features	Clinical Features
Central Conventional Chondrosarcoma	IDH1 or IDH2 mutation	Most common type (approx. 70%); may arise from enchondroma or Ollier's disease; arises in pelvis, humerus, femur, or ribs; chemotherapy and radiotherapy resistant
Peripheral Conventional Chondrosarcoma	IDH1 or IDH2 mutation	Rare (approx. 10%); always arise from osteochondroma; younger individuals; arise in pelvis or shoulder; chemotherapy and radiotherapy resistant
Periosteal Conventional Chondrosarcoma	Not EXT, possibly Hedgehog pathway activation	Very rare (approx. 1%); younger individuals; distal femur or humerus; prognosis better than other histologies; chemotherapy and radiotherapy resistant
Mesenchymal Chondrosarcoma	HEY1-NCOA2	Very rare (approx. 2%); younger individuals, arise in head/neck, vertebrae, ribs, pelvis; round cell component is chemotherapy and radiotherapy sensitive
Dedifferentiated Chondrosarcoma	IDH1 or IDH2 (50% of cases)	Rare (approx. 10%); arise in conventional chondrosarcoma; older individuals; arise in femur and pelvis; High grade by definition; low response rates to chemotherapy

to affect patients between age 50 and 70, with no particular gender predilection. Clinically, patients present with pain (85% of cases), followed by pathologic fracture (31%) and a soft-tissue mass (29%).[29] The majority of tumors occur centrally in medullary bone usually affecting the pelvis, femur, and humerus.[6,30] Dedifferentiated chondrosarcoma is a high-grade malignant neoplasm usually with the histologic appearance of an osteosarcoma, an undifferentiated high-grade pleomorphic sarcoma or fibrosarcoma that arises in a pre-existing conventional chondrosarcoma.[11,31,32] Unusual histologies, such as squamous cell carcinoma, have been reported.[33] The pathogenesis of dedifferentiated chondrosarcoma remains incompletely understood. It has been postulated that the high-grade noncartilaginous component arises in a long-standing low-grade cartilaginous element.[33,34] Dedifferentiated chondrosarcomas are highly aggressive tumors with a grim prognosis. In a multicenter review of 337 patients, 71 (21%) had metastases at the time of diagnosis with only 10% survival at 2 years.[35] Systemic chemotherapy with poor-prognosis osteosarcoma regimens is often used, but unlike traditional osteosarcoma, response rates to chemotherapy are only 20%.[36] Moreover, therapy with high-dose ifosfamide-containing regimens are slightly superior with 33% survival at 2 years, but only 15% at 5 years.[37]

Mesenchymal Chondrosarcoma

Mesenchymal chondrosarcoma is a rare high-grade malignant cartilaginous tumor that may originate in either bone or soft tissue (dura).[6] These tumors are characterized by a bimorphic cellular pattern that is composed of islands of differentiated cartilage and highly cellular areas that are composed of undifferentiated small round blue cells.[11] Unlike other chondrosarcoma subtypes, the median age at presentation is age 25 and extraosseous tumors are observed.[38] The principal symptoms are pain and swelling. Mesenchymal chondrosarcoma most commonly arise in the craniofacial bones, ribs, ilium, and the vertebrae.[11,39] The meninges are one of the most common sites of extra skeletal involvement.[40] The overall prognosis is poor for conventional chondrosarcomas. Approximately 20% have metastatic disease at diagnosis.[39] Reported 10-year survival rates are 10 to 20%.[41] However, approximately 30% of mesenchymal chondrosarcomas will respond to Ewing sarcoma-type chemotherapy regimens, with evidence of improved survival as a result.[36,38,39]

Clear Cell Chondrosarcoma

Clear cell chondrosarcoma is a rare low-grade subtype of chondrosarcoma that is characterized histologically by bland clear cells in addition to hyaline cartilage.[6,11] Less than 2% of chondrosarcomas are classified as clear cell histology. Men are almost three times more likely to develop clear cell chondrosarcoma than women and most patients are between age 25 and 50.[42] Approximately two-thirds of lesions occur in the humeral or femoral head.[42] Although clear cell chondrosarcomas are low-grade tumors, partial excision or curettage leads to recurrence in at least 70% of the cases, and it should be avoided.[43,44] Local excision commonly is curative. The overall recurrence rate is 16%, and approximately 15% of patients die of the disease. Metastases to the lung, brain, and bones have been reported.[11] These tumors do not respond to chemotherapy or radiation; surgical resection is the only known therapy.

Myxoid Chondrosarcoma

Primary skeletal myxoid chondrosarcoma is a rare neoplasm. It remains unclear whether this constitutes a separate clinicopathologic entity or if it is part of the spectrum of conventional chondrosarcoma with prominent myxoid stroma.[23] Histologically, myxoid chondrosarcoma of bone has similar characteristics to the extraskeletal myxoid chondrosarcoma (EMC), but these are two distinct diagnoses.[45]

Extraskeletal myxoid chondrosarcoma is a malignant soft-tissue tumor characterized by a multinodular architecture, abundant myxoid matrix, and malignant chondroblast-like cells.[11,46,47] Typically, EMC has a characteristic translocation, t(9;22)(q22;q12.2), fusing EWSR1 to NR4A3 (genes formerly termed EWS and CHN, TEC, or NOR1, respectively).[48-51] A small proportion of EMC have a different translocation, t(9;17)(q22;q11.2), which results in a RBP56-NR4A3 fusion gene and neuroendocrine differentiation in some cases.[51] Given that these tumors can arise in the extremities and may mimic chondrosarcoma, this is an instance in which genetic testing for the translocation can affect therapy

greatly. A recent retrospective study showed prolonged overall survival in patients with extraskeletal myxoid chondrosarcoma despite high rates of local and distant recurrence.[52] Although anthracycline chemotherapy has not been effective historically, recent reports of clinical responses from sunitinib are encouraging for patients with metastatic disease.[53]

TREATMENT CONSIDERATIONS

As previously discussed, understanding the histologic subtype and grade of chondrosarcoma is helpful in predicting biologic behavior. However, regardless of subtype, surgical resection remains the cornerstone of therapy with the best potential for cure of primary chondrosarcoma.[9]

Several retrospective studies have shown that wide excision with negative margins is associated with higher event-free survival and overall survival rates for patients with large tumors and pelvic localization, regardless of the histologic grade.[54,55] A meta-analysis published in 2011 showed that in select patients with low-grade, nonpelvic chondrosarcomas, intralesional excision may be used as an alternative to wide excision without affecting outcomes.[56] In general, the recommended approach by the National Comprehensive Cancer Network Guidelines (Bone Sarcoma Version 1.2015) is wide local excision of the chondrosarcoma for any intermediate or high-grade histologies, large tumor size, pelvic locations, and intra-articular or soft-tissue involvement. This should be performed in a high-volume sarcoma center with experienced orthopedic oncologists.

Chondrosarcomas are relatively radiotherapy (RT)-resistant. Currently, there is not enough data to support its routine use in patients with this disease. However, RT may be considered if there is incomplete resection, for palliation of symptoms, in patients with advanced or unresectable tumors, or for mesenchymal chondrosarcoma.[57] In a large series involving 229 patients with chondrosarcomas of the skull base, the combination of proton and photon beam RT resulted in a sustained local control rate in most patients.[58]

The role of chemotherapy in the treatment of patients with chondrosarcoma remains unclear and should be considered on a case-by-case basis. At our center, we generally reserve chemotherapy for dedifferentiated and mesenchymal subtypes for patients with reasonable performance status.

Although the vast majority of patients with recurrent or metastatic chondrosarcoma do not respond to conventional sarcoma chemotherapy regimens, there are anecdotal reports of successful treatment with doxorubicin-based regimens, single-agent ifosfamide or methotrexate.[36,59-61]

The mechanisms contributing to resistant to chemotherapy that are seen in chondrosarcomas are not fully understood. It has been suggested that because of avascular matrix and often a low percentage of dividing cells, these tumors have a poor response to chemotherapy that targets cycling cells.[57] In the case of mesenchymal chondrosarcoma, the majority of the tumor may be composed of well-differentiated chondrosarcoma cells and cartilaginous matrix. Thus, there

may be little shrinkage even when the chemotherapy was efficacious against the small round blue cell component of the biphenotypic tumor cells. It also has been suggested that the expression of P-glycoprotein plays a role in resistance to chemotherapy. P-glycoprotein is encoded by the gene multidrug resistance-1 (*MDR-1*) and is expressed by chondrosarcoma cells.[62] It has been demonstrated that the expression of *MRD-1* in human chondrosarcoma cell lines results in resistance to doxorubicin in vitro.[63]

### Targeted Therapy for Chondrosarcoma

Within the last several years, there has been increased interest in exploring targeted therapies for chondrosarcomas. Our understanding of pathways implicated in chondrosarcomas is reviewed by Samuel et al.[64] As outlined in their work, one can consider the early and late genetic events that lead to the development of chondrosarcomas to design potential pathways that may be amenable to inhibition.

The indian hedgehog (IHH)/parathyroid hormone-related peptide pathway (PTHrP) is critical to chondrocyte maturation and development, and constitutive IHH signaling has been demonstrated in chondrosarcomas. Based on upregulation of intramembrane receptor patched (PTCH) and downstream transcription factors, including GLi, clinical trials were conducted with GDC-0449. Unfortunately, medical progression-free survival was short at 3.5 months and further enrollment on the study was halted.[65]

Another pathway of interest in chondrosarcoma was PI3K/mTOR, based on observations of increased receptor-type tyrosine kinase activity, including high levels of phosphorylated S6 and marked in vitro response to BEZ235, a PI3K/mTOR inhibitor.[66] In a recent retrospective analysis, 10 patients with unresectable recurrent chondrosarcoma received the combination of sirolimus/cyclophosphamide. The chemotherapy was well tolerated and resulted in a disease control rate of 70% (10% of patients had objective response and 60% of patients had stable disease for at least 6 months).[67] Based on these findings, further exploration of mTOR inhibition is warranted.

Activation and/or overexpression of PDGFR-alpha (PDGFRA) and PDGFR-beta (PDGFRB) has been described in conventional chondrosarcomas, but activating mutations have not been found.[68] Unfortunately, trials have failed to show significant clinical activity.[69]

Finally, another mechanism with interesting preclinical results in chondrosarcomas focuses on targeting epigenetic regulatory mechanisms via histone deacetylase inhibitors. Several studies have revealed the key roles played by acetylation or deacetylation in specific gene expressions of chondrocytes.[70,71] Further research revealed that HDAC inhibitors cause a variety of phenotypic changes, such as cell cycle arrest, morphologic reversion of transformed cells, apoptosis, and differentiation.[72,73] Sakimura et al recently reported the inhibition of tumor growth and the induction of differentiation of chondrosarcoma cells using the HDAC inhibitor depsipeptide.[74] Because of the promising results, several HDAC inhibitors currently are being used in clinical trials.

FIGURE 1. The Metabolic Effect of *IDH* Mutation in the Krebs Cycle
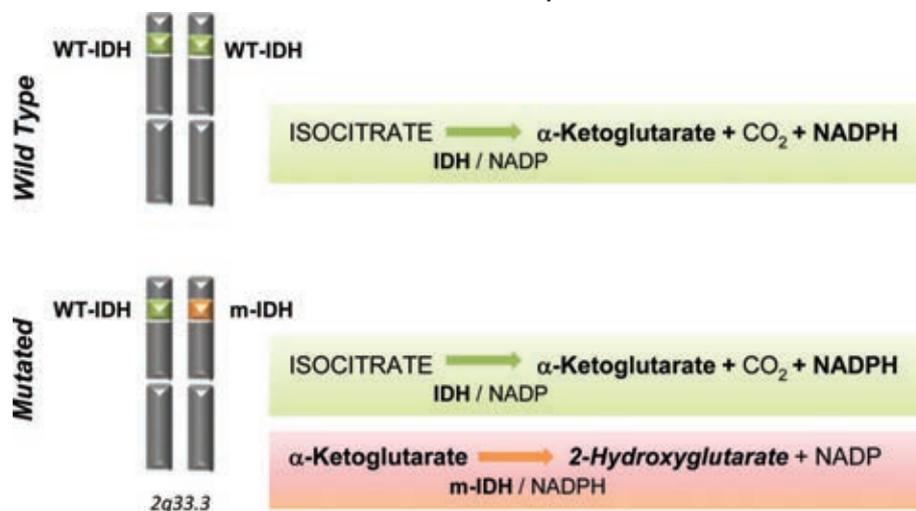
The wild-type IDH protein continues to produce alpha-ketoglutarate (KG); however, the mutant IDH protein converts KG to 2-Hydroxyglutarate (2-HG). HG then is able to function as an oncometabolite in chondrosarcomagenesis.

Inhibitors of IDH 1/2 Mutant Proteins

Perhaps the most exciting therapy on the horizon for patients with chondrosarcoma is the development of inhibitors of isocitrate dehydrogenase (IDH) enzymes. Isocitrate dehydrogenase proteins consist of three regulatory enzymes (IDH1, IDH2, and IDH3) that catalyze the $NADP^+$-dependent oxidative decarboxylation of isocitrate (ICT) into alpha-ketoglutarate (alpha-KG) in the Krebs cycle (Fig. 1).[75] IDH1 is found in both peroxisomes and the cytosol,[76,77] whereas IDH2 is a mitochondrial isoform of IDH.[78] The genes encoding IDH1 and IDH2 are located on chromosome 2q33.3[79] and 15q26.1,[80] respectively.

Mutations in the *IDH* family of genes recently have been described in patients with a variety of cancers. The mutation in the *IDH1* gene was first discovered in colorectal cancers.[81] Soon afterwards, somatic mutations affecting *IDH1* or *IDH2* were detected in more than 70% of grade 2 to 3 gliomas and secondary glioblastomas.[82] More recently, alterations in these genes were identified in many other types of cancers, including acute myeloid leukemia, cholangiocarcinomas, and chondrosarcomas.[83,84] Somatic mutations also have been identified in up of 87% of benign enchondromas, up to 70% of primary conventional central chondrosarcomas, and 54% of dedifferentiated chondrosarcomas.[28,85,86]

IDH1/2 mutations are heterozygous and affect a single arginine residue. The mutations in the IDH proteins frequently lead to changes affecting arginine-132 (R132H or R132C) in IDH1[87-89]; arginine-140 (R140Q) is the most common change seen in IDH2.[90] Mutated IDH1 or IDH2 are active catalytic enzymes. However, their mutations cause a reduced capacity to convert ICT to alpha-KG and an acquired ability to convert alpha-KG to delta-2-hydroxyglutarate (2-HG), which is considered an oncometabolite[75,91-94] (Fig. 1). Typically, the alterations in *IDH1* and *IDH2* are mutually exclusive and occur at very early stages of tumor development.[95]

The exact mechanism by which accumulation of 2-HG may lead to tumor formation remains unknown. However, recent publications suggested a possible epigenetic mechanism.[82,96-99] 2-HG inhibits the function of alpha-KG-dependent enzymes such as ten-eleven translocation gene family (*TET*) 2 by competing with alpha-KG.[100] Moreover, experiments using glioma lines showed that 2-HG inhibits both the TET of 5-methylcytosine hydroxylases and the H3K9 demethylase KDM4C, causing global DNA hypermethylation and leading to transcriptional blockages.[96,98] Also, it was recently described that IDH mutations induce a global hypermethylated phenotype that is distinctive of the gliomas with these mutations.[101]

In normal cells, 2-HG is present in low levels. However, IDH1/IDH2 mutations in cancer cells result in excess of production and accumulation of 2-HG.[92,99] Different tumor types, including glioma and acute myelogenous leukemia, have described elevated 2-HG compared to cells with wild-type alleles.[94,102] Fathi et al reported that 2-HG levels in serum, urine, bone marrow, and myeloblasts were significantly higher ($p < 0.0001$) in patients with acute myeloid leukemia with mutant *IDH* compared to wild type, and showed that serum and urine 2-HG decreased with response to treatment.[103] In chondrosarcoma, we have shown previously that 2-HG also can be detected in serum and urine of a patient with IDH2-mutant dedifferentiated chondrosarcoma (Li et al, unpublished data, November 2014). We also demonstrated that in vitro treatment of IDH1 mutant chondrosarcoma cell lines with an IDH1 inhibitor decreased production of 2-HG, induced apoptosis, and inhibited tumorigenic activity. Thus, it appears that 2-HG is a noninvasive biomarker of treatment response, and mutant IDH is being used as a predictive biomarker to select patients for enrollment in clinical trials of novel IDH inhibitors (NCT00989261, NCT02074839, NCT02073994, NCT02273739). Although, preliminary data in leukemia patients treated with IDH inhibitor suggests considerable efficacy, the results from the solid tumor study including chondrosarcoma are too early to characterize.

CONCLUSION

Chondrosarcomas are a unique, rare family of neoplasms that pose substantial treatment challenges, particularly in the metastatic and refractory setting. The next few years are likely to shed light on the unique biologic nature of these diseases, with development of novel therapies. Given the limited response to chemotherapy and other systemic drugs, referral of patients to clinical trials, particularly in the setting of documented *IDH*-mutated disease, should be a priority.

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Chemotherapy for Bone Sarcomas in Adults: The MD Anderson Experience

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OVERVIEW

Increasing age is an adverse prognostic factor in the treatment of primary bone tumors. There are few published data on treatment of primary bone tumors in adults. This paper presents data from the Department of Sarcoma Medical Oncology at The University of Texas MD Anderson Cancer Center, summarizing our treatment results. To treat primary osteosarcoma, we used 90 mg/m^2 of doxorubicin as a continuous intravenous infusion over 48 to 96 hours and 120 to 160 mg/m^2 of cisplatin intravenously or intra-arterially. Initially, we found a marked difference in postoperative continuous disease-free survival (CDFS) between those with 90% or greater (i.e., good response) tumor necrosis and those with less than 90% (i.e., poor response) tumor necrosis. The sequential addition of high-dose methotrexate and ifosfamide to patients with poorly responding disease improved their CDFS to that of patients with good response. Older patients and those who have tumors with variant histology have inferior outcomes. Evaluation of subsequent patients revealed similar outcomes for those with good or poor response to induction therapy, supporting our practice of adaptation of postoperative chemotherapy to the results of preoperative chemotherapy. PET-CT is the best imaging modality to screen for a response with tumors inside bone. To treat Ewing sarcoma, we have employed 2 mg of vincristine, 75 to 90 mg/m^2 of doxorubicin as a 72-hour infusion, and 2.5 g/m^2 of ifosfamide over 3 hours daily for 4 doses (i.e., vincristine, doxorubicin, and ifosfamide [VAI]). Preliminary analysis indicates a higher CDFS when adjusted for patient age than seen with the standard alternating regimen used in pediatrics. A screening MRI of the pelvis and spine can detect subtle metastatic disease in bone or bone marrow that is missed by other imaging modalities or blind biopsy. Chondrosarcoma is treated surgically or on investigational protocols. Giant cell tumor of bone is usually managed surgically, but multiple options exist for medical treatment, and therapy is individualized with embolization, denosumab, and interferon.

Increasing age is an adverse prognostic factor in the treatment of primary bone tumors.[1-3] There are few, if any, randomized studies that address the treatment of primary bone tumors in adults, and no data support the common practice of extrapolating from the results of pediatric trials to the adult population. We know from pediatric studies that conclusions based on data derived from patients younger than 18 do not always apply to those age 18 or older. We know, for example, from the data presented at American Society of Clinical Oncology, that compressed VDC-IE (vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide) was not more effective against Ewing sarcoma in patients older than age 17 than standard dosing, but, because those patients were included in the study, the overall results are extrapolated to apply to them.[3] The therapies that we will describe are derived from the experience of our group in the Department of Sarcoma Medical Oncology at The

University of Texas MD Anderson Cancer Center and are based on a sound rationale for individual regimens rather than on randomized trial data showing the superiority of any one regimen over another. Traditionally at our institution, adult patients were at least age 16. In recent years, the age of the pediatric service has expanded, and the majority of patients in the age range of 16 to 21 years are seen in pediatrics.

The two most common pediatric bone sarcomas, osteosarcoma and Ewing sarcoma, are seen in adults as well. In addition, chondrosarcoma, unclassified pleomorphic sarcoma (UPS, previously called MFH) of bone, and giant cell tumor of bone are seen mostly in adults.

CHONDROSARCOMA

Fortunately, because no systemic therapy has proven effective, most patients with conventional chondrosarcoma have

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local disease only and can be treated effectively with surgery. Conventional chondrosarcomas are divided into central chondrosarcomas, which arise from enchondromas, and peripheral chondrosarcomas, which arise from osteochondromas. The majority of chondrosarcomas are central chondrosarcomas.[4] Patients with metastatic disease usually are treated only on investigational protocols, which have not yet generated positive data. Preclinical data implicate the hedgehog pathway in the development and proliferation of chondrosarcoma cells.[4,5] A clinical trial of the hedgehog inhibitor GDC-0449 did not meet its objectives, however.[6] The presence of frequent mutations of *IDH1* and *IDH2* in central chondrosarcomas[7] suggests a new target for therapy. We await clinical data.

We treat dedifferentiated chondrosarcoma, a composite tumor with a low-grade chondrosarcoma juxtaposed to a high-grade osteosarcoma or UPS of bone-like osteosarcoma. Dedifferentiated chondrosarcoma has a dismal prognosis when treated by surgery alone; all patients experienced disease relapse within 1 year, and all but one were dead within 2 years.[8] We noted a 51% relapse-free survival in a 15-patient series treated as if they had osteosarcoma (vide infra).[9] We treat mesenchymal chondrosarcoma, a composite tumor with a low-grade chondrosarcoma juxtaposed to a malignant small round cell tumor, like Ewing sarcoma. Although we have not analyzed our data, obvious responses to therapy have been noted. In support of our strategy, a recent review by Italiano et al,[10] which observed 180 patients treated with chemotherapy in 15 institutions in Europe and the United States, noted a response rate of 31% for mesenchymal chondrosarcoma, 20.5% for dedifferentiated chondrosarcoma, only 11.5% for conventional chondrosarcoma, and 0% for clear cell chondrosarcoma.[10]

KEY POINTS

- Older patients with osteosarcoma and Ewing sarcoma have inferior outcomes than pediatric patients.
- To treat osteosarcoma, induction chemotherapy with doxorubicin and cisplatin permits administration of full doses of both agents.
- Unlike some pediatric studies, our data support the addition of ifosfamide as well as high-dose methotrexate to poor responders but do not support the routine use of high-dose methotrexate for all patients.
- Our data suggest that vincristine, doxorubicin, and ifosfamide is a good choice of primary chemotherapy for Ewing sarcoma.
- PET-CT is the best imaging modality to assess response, especially in osteosarcoma, but MRI is the most sensitive method to detect subtle metastases in bone or bone marrow.

GIANT CELL TUMOR OF BONE

Giant cell tumor of bone is a fascinating tumor. Although histologically benign, approximately 2% of tumors can metastasize.[11] The metastases also are histologically benign. Histologic malignant transformation (dedifferentiation) may occur spontaneously or, more commonly, after radiation therapy. Although pathologists refer to giant cell tumor of bone as a benign tumor, we consider it a low-grade malignancy, analogous to (or worse than) well-differentiated liposarcoma or grade 1 chondrosarcoma, which cannot be distinguished histologically from their benign counterparts but which do not metastasize without further malignant change. In the majority of occurrences, intralesional resection (curettage and instillation of polymethyl methacrylate) is curative, whereas en bloc resection is preferred for lesions in expendable bones or those extending into soft tissue.[12] Until recently, medical oncologists have rarely been involved in the management of this tumor, seeing only the occasional patient with metastatic disease or with a primary tumor in the spine or sacrum, where resection would cause excessive morbidity. We prefer to avoid the use of radiation therapy because it has been associated with secondary malignancy, but we have used it when there are no reasonable alternatives. This should be even less necessary in the future.

Giant cell tumors are highly vascular lesions, and we have treated sacral lesions with arterial embolization since the 1970s.[13] Therapy is effective in approximately 50% of the cases, and long-term follow-up times show that most patients whose tumors respond are essentially cured.[14] Since 1992, we have treated patients who experience disease progression after embolization or those who have metastatic disease with interferon alfa.[15] It was the only antiangiogenic agent available at the time,[16] and, like embolization, it is effective in approximately 50% of the cases and has curative potential.[14] Interestingly, we have noted delayed responses to therapy after clear progression, sometimes only after the therapy has been discontinued.

The biology of giant cell tumor of bone is now much better understood.[17] The tumor cells (or malignant cells) are stromal cells with an immature osteoblast phenotype. These cells secrete RANKL (RANK ligand, a member of the tumor necrosis factor [TNF] family), a key mediator of osteoclast biology. Under RANKL signaling, the tumor cells recruit monocyte precursors that are transformed into osteoclast-like giant cells that represent the bulk of the actual giant cell tumor. Denosumab, a fully human monoclonal antibody that selectively binds RANKL, has been highly effective in the treatment of giant cell tumor of bone; 86% of patients experienced objective evidence of response in the initial phase II study[18] and, in the larger expansion study, 72% of patients responded likewise.[19] Because denosumab does not treat the malignant cell directly, however, it is unclear whether life-long therapy

FIGURE 1. Continuous Disease-Free Survival by Tumor Necrosis

FIGURE 2. Continuous Disease-Free Survival with Tumor Necrosis of 90% or Less
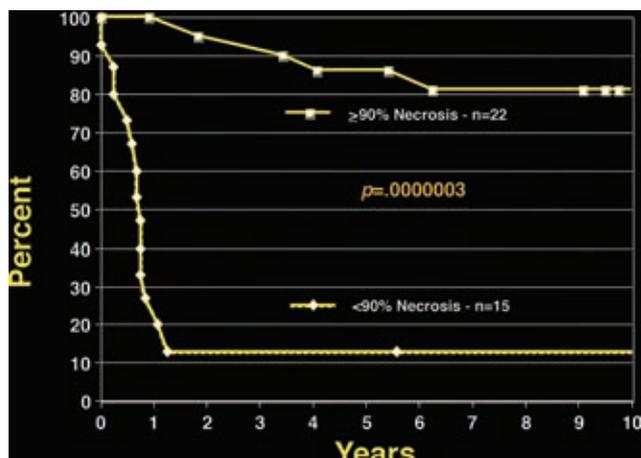
will be needed in patients whose disease cannot be treated surgically.[17]

OSTEOSARCOMA

Our therapy for osteosarcoma is based on experience in a group of patients treated from 1980 to 1991 with induction therapy of 90 mg/m^2 of doxorubicin as a continuous intravenous infusion over 48 to 96 hours and 120 to 160 mg/m^2 of cisplatin intra-arterially. Initially, we found a marked difference in postoperative continuous disease-free survival (CDFS) between those with 90% or greater (i.e., good) tumor necrosis and those with less than 90% (i.e., poor) tumor necrosis.[20] (Fig. 1) We subsequently modified postoperative chemotherapy, first adding high-dose methotrexate and later, in addition, ifosfamide. We found no benefit from the addition of methotrexate to the good responders, but we observed an increased CDFS in the poor responders from 13% to 34%. The subsequent addition of ifosfamide to the postoperative regimen further increased the CDFS to 67% (Fig. 2), such that the difference between good and poor responders was no longer statistically significant.[21]

Because we have not had additional good drugs to add to our regimen, we have continued the practice established in our 1988 to 1991 series of adding ifosfamide and high-dose methotrexate to patients who have poor tumor necrosis. We recently reviewed a series of 46 patients with primary osteosarcoma of the extremities who were treated according to this approach. The median 10-year CDFS was 50%, and there was no difference between patients with good or poor necrosis. The recent EURAMOS study concluded that addition of ifosfamide was of no benefit to (largely) pediatric patients with osteosarcoma and poor necrosis.[22] The initial approach with modified adjuvant chemotherapy after poor response to neoadjuvant chemotherapy came from the sequential studies of Rosen et al,[23]
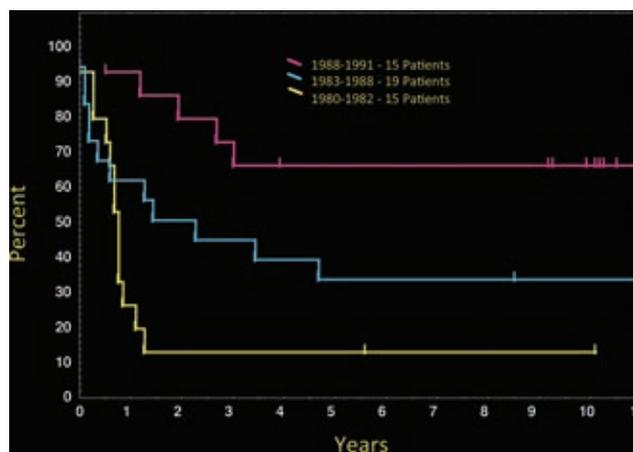
the inventor of the neoadjuvant approach.[23] Our data, together with the early studies of Bacci et al from the Rizzoli Institute,[24] support adaptation of postoperative therapy to preoperative response, despite the EURAMOS data. Our approach emphasizes maximum doses of the individual drugs in the initial doxorubicin-cisplatin doublet rather than adding methotrexate, which overlaps in nephrotoxicity with cisplatin and in mucositis with doxorubicin. We see no advantage to adding methotrexate in good responders, and it can be a difficult drug to use in older patients.

One factor that needs emphasis is that the spectrum of histologic appearance in adult osteosarcoma is quite different from that usually seen in pediatric series. Conventional osteosarcoma (osteoblastic, chondroblastic, and fibroblastic subtypes) makes up the vast majority of cases in typical pediatric series. Of the variants, only telangiectatic osteosarcoma has a similar response to therapy and prognosis. Patients with chondroblastic osteosarcoma had a lower rate of good necrosis but a better prognosis despite poor necrosis in our original series of patients, and that observation appears to be true in the subsequent group we analyzed, albeit with small numbers. Patients with variant histology (dedifferentiated parosteal osteosarcoma, high-grade surface osteosarcoma, small cell osteosarcoma) other than telangiectatic osteosarcoma represented 12% of our original series and had significantly worse CDFS. Perhaps because of the increasing age of patients currently seen on our pediatric service, variant histology was even more common in our recent group (28%). The patients in our current group were older than in our original series. In our current group, 46% are older than age 30, and 33% are older than age 40, compared with 23% and 11%, respectively, in our initial series.

PET-CT is the best imaging modality to assess response to therapy. MRI is the best modality to define an anatomic abnormality within bone, but it routinely overestimates the extent of residual viable tumor. CT shows details of cortical

structure and calcification in the soft tissue, so combining the CT images from the PET-CT with the MRI gives the best overall assessment.

Until recently, new agents with clear activity in the treatment of metastatic osteosarcoma have not been identified in the past 2 decades. Anecdotal evidence for the efficacy of gemcitabine with or without docetaxel was not confirmed in a clinical trial.[25] Recently, however, Grignani et al[26] reported a study from the Italian Sarcoma Group using the combination of sorafenib and everolimus.[26] The median progression-free survival (PFS) was 5 months, with a 6-month PFS rate of 45% despite an objective response rate of only 10%. It has long been known that primary osteosarcoma may not shrink when it responds. The use of PFS as an endpoint in this study is novel and important, and it throws into question some of the negative clinical trials of the past.[25]

EWING SARCOMA

It is even harder to find studies on Ewing sarcoma in adults than it is to find studies on osteosarcoma. Our initial data on the treatment of Ewing sarcoma in adults is, unfortunately, published only in abstract form,[27] and the logistics of transition from paper to electronic medical records and film to digital images makes a new review of the data cumbersome at best. The major lessons from our initial patients treated with VAdriaC (vincristine, doxorubicin, and cyclophosphamide) or CyVADIC (cyclophosphamide, vincristine, doxorubicin, and dacarbazine) were that any residual viable tumor in excess of scattered cells carried a high risk of recurrence and that, the more doxorubicin given, the better the patients faired. Therefore, it has become our practice to add additional postoperative chemotherapy with an alternative regimen to any patient who has less than 99% tumor necrosis.

The role of ifosfamide, questioned in the treatment of osteosarcoma, is well established in the treatment of Ewing sarcoma in pediatrics.[2,3] Because ifosfamide is one of the most active agents in the treatment of adult sarcomas, we have considerable experience in its use. The standard soft tissue sarcoma chemotherapy regimen is doxorubicin and ifosfamide, which we have studied extensively.[28] Ifosfamide is superior to cyclophosphamide in the treatment of sarcomas,[29] so we saw no reason to alternate cyclophosphamide with ifosfamide and have thus adopted VAI as our primary treatment regimen for Ewing sarcoma by simply adding vincristine to our standard soft tissue sarcoma regimen. We give 2 mg of vincristine on day 1, 75 to 90 mg/m^2 of doxorubicin as a 72-hour infusion, and 2.5 g/m^2 of ifosfamide over 3 hours daily for four doses.

We reviewed the data on a series of 24 patients with primary Ewing sarcoma of bone treated with VAI. The median age was 23 (range, 17 to 54); 17% of patients were younger than 20, and 17% of patients were older than 30. The 5-year CDFS was 70%, and all relapses but one occurred within 1 year of treatment. The primary sites of relapse were local recurrence in bone and adjacent soft tissue, with only a single case of pulmonary metastasis as

the first site. Two patients experienced relapse during induction therapy. No patient who experienced relapse survived. Twenty of the 24 patients underwent surgery after induction chemotherapy. Eleven patients (55%) who had more than 95% tumor necrosis in the resected specimen had an 80% 5-year CDFS compared with a 44% 5-year CDFS for the nine patients (45%) who had less than 95% tumor necrosis. All patients with more than scattered residual tumor cells after induction therapy underwent variable consolidation chemotherapy, including high-dose ifosfamide, ifosfamide/etoposide (IE), and irinotecan/temozolomide with or without vincristine. Although this is a small series, the results compare favorably with the commonly used regimen of alternating VAdriaC and IE used in the pediatric literature, for which event-free survival for patients older than age 18 was 44%[2] and was 47% in the study of compressed-interval dosing.[3]

MRI is the best modality to define an anatomic abnormality within bone or bone marrow. A screening MRI of the spine and pelvis can detect subtle metastatic sites missed by other imaging modalities, even PET-CT, or blind bone marrow biopsies. PET-CT is the best imaging modality to assess response to therapy, but it is not as critical as in osteosarcoma, because Ewing sarcoma tends to shrink or disappear as it responds.

New approaches to the therapy of Ewing sarcoma with insulin-like growth factor 1 receptor (IGF-1R) blockade with[30] or without[31] mammalian target of rapamycin inhibitors hold some promise, but thus far have been effective in only a minority of patients. Unfortunately, the IGF-1R target has relatively little interest to most pharmaceutical companies, and further studies to select the subset of patients who might benefit most have been stymied by the lack of drug supply and pharmaceutical support. Other new approaches, interesting from a theoretical point of view, have yet to undergo formal study.

CONCLUSION

Treatment of primary bone tumors in adults presents challenges and opportunities. The first challenge is finding effective therapy for chondrosarcomas. These tumors are like the gastrointestinal stromal tumors of the 1990s. We have no medical treatment. There are some interesting targets. How do we turn it around? For giant cell tumor of bone, we have a wonderful new agent, but is it curative? How long does therapy need to continue? How can we take advantage of the great activity of denosumab to design better treatments for the future? In treating osteosarcoma and Ewing sarcoma in adults, we do not do as well as our pediatric colleagues, perhaps because younger patients can tolerate more intensive chemotherapy and perhaps because of the differing mix of variant histologies. The VAI regimen for Ewing sarcoma seems promising, but formal studies and larger numbers will be required. The tragedy of near certain death with relapse in Ewing sarcoma needs to be addressed with better strategies, perhaps aimed at directly inhibiting the effects of its causative translocation.

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SARCOMA

Well-Differentiated and Dedifferentiated Liposarcoma: New Challenges and New Directions

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Application of Molecular Biology to Individualize Therapy for Patients with Liposarcoma

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OVERVIEW

Liposarcomas are one the most common of over 50 histologic subtypes of soft tissue sarcomas that are mostly resistant to chemotherapy. Histologically, liposarcomas themselves are heterogeneous and fall into four distinct subtypes: well-differentiated/atypical lipomatous tumor, dedifferentiated liposarcoma, myxoid (round cell) liposarcoma, and pleomorphic liposarcoma. Surgical resection with negative margins remains the mainstay for definitive treatment for operable disease. For unresectable disease, retrospective studies have identified myxoid (round cell) and pleomorphic sarcomas to be relatively responsive to chemotherapy. Recent studies have identified distinct genetic aberrations that not only aid in the diagnosis of particular liposarcoma subtypes, but represent actionable targets as they are considered central to disease pathogenesis. Cyclin-dependent kinase 4 (CDK4) and murine double minute 2 (MDM2) are overexpressed in well-differentiated and dedifferentiated liposarcomas and offer tantalizing opportunities that are being pursued in clinical trials. Myxoid (round cell) liposarcomas appear to be sensitive to trabectedin, which is currently under U.S. Food and Drug Administration (FDA) review. Liposarcomas do not represent a uniform disease and understanding the underlying molecular mechanism will help not only in accurate diagnosis but in selecting the appropriate treatment.

Soft tissue sarcomas (STS) are a complex heterogeneous collection of more than 50 neoplasms of mesenchymal origin. According to the American Cancer Society, in 2015 approximately 11,930 patients in the Unites States will be diagnosed with STS, and nearly 4,870 will die from the disease. Surgery is the mainstay of therapy. For metastatic STS, cytotoxic chemotherapeutic agents such as doxorubicin or gemcitabine plus docetaxel have been used with response rates of approximately 25%, and overall survival (OS) of 12 to 18 months.[1,2] Whenever possible, treatments are now tailored to the histologic subtype, tumor characteristics, molecular signature, and patient performance status. Liposarcoma is among the most common sarcoma subtypes, with average annual, age-adjusted incidence of 0.4 to 1.1 per 100,000 persons dependent on gender and race.[3] Liposarcomas are a heterogeneous group of adipocytic neoplasms that are generally resistant to chemotherapy. This review will focus on management of liposarcomas and discuss novel targets and therapies directed toward them that are being tested in clinical trials.

LIPOSARCOMAS

Liposarcomas are neoplasms of adipocytes that normally grow slowly and present as a painless nonulcerated enlarging mass. They are subclassified into distinct categories dependent on their histology, molecular signature, and behavior[4]:

- Well-differentiated/atypical lipomatous tumor
- Dedifferentiated liposarcoma
- Myxoid (round cell) liposarcoma
- Pleomorphic liposarcoma
- Liposarcoma, not otherwise specified

Rarely, a specimen may have a combination of morphologic subtypes; this is referred to as mixed liposarcoma.

ATYPICAL LIPOMATOUS TUMOR/WELL-DIFFERENTIATED LIPOSARCOMA

Atypical lipomatous tumor (ALT) or well-differentiated liposarcoma (WDLS) is the least aggressive of the malignant forms of liposarcoma and represents 40% to 45% of the liposarcomas that are diagnosed.[5] Microscopically, they consist of scattered lipoblasts with a single atypical nucleus surrounded by large intracytoplasmic vacuoles in a background of adipocytes.[4] ALT/WDLS are usually indolent and tend not to metastasize, but can recur locally. However, if they undifferentiate into the dedifferentiated form, they exhibit an aggressive phenotype and are likely to metastasize.[6] The retroperitoneum and extremities are common primary sites, but they can also occur within the mediastinum and parates-

ticular region.[7] ALT/WDLS within the retroperitoneum, mediastinum, and spermatic cord are more likely to recur and result in significant morbidity and mortality from local disease.[6] Gene expression profiling when compared to normal fat has indicated overexpression of several genes in the 12q12–15 amplicon, including *CDK4* and *MDM2*.[7] MDM2 is a ubiquitin ligase that binds to the transactivation domain of p53 and promotes its degradation.

DEDIFFERENTIATED LIPOSARCOMA

Dedifferentiated liposarcoma (DDLS) is the second most common type of liposarcoma diagnosed. DDLS is cellular and consists of nonlipogenic sarcoma that transitions abruptly within an ALT.[4] DDLS has morphologic and molecular similarities to ALT/WDLS but behaves aggressively. DDLS has a higher rate of recurrence, with 20% to 30% distant metastasis, and a 6-fold higher risk of death compared to ALT/WDLS.[8,9] Many of the gene alterations found in WDLS are also found in DDLS.[7] For example, both *CDK4* and *MDM2* are overexpressed in both of these diseases. Genomic alterations of 207 STS, which included 50 DDLS specimens, confirmed the prior findings of amplifications within 12q12–15, including *CDK4* and *MDM2*.[10] WDLS and DDLS respond very poorly to chemotherapy and new treatment options are desperately needed.[11]

CDK4 and MDM2 Inhibitors

CDK4−Palbociclib. CDK4 is amplified in more than 90% of WDLS and DDLS cases, making it an opportune target in this disease subtypes. Preclinically, palbociclib (PD0332991), a CDK4/6 inhibitor, induces a G1 cell cycle arrest in liposarcoma cell lines that overexpress CDK4.[10] A phase I trial with palbociclib in patients with advanced solid malignancies identified one patient each with ATL/WDLS and DDLS who

had stable disease lasting several years at a dose of 200 mg daily for 14 consecutive days in 21-day cycles.[12] This led to an open-label phase II trial for patients with WDLS and DDLS. Patients' tumors were required to have CDK4 amplification and retinoblastoma protein (RB) expression, which is the downstream target for CDK4. Preclinically, RB expression was required for palbociclib activity.[10] Among the 30 patients enrolled (five with WDLS and 25 with DDLS), the trial reported a 12-week progression-free survival (PFS) rate of 66%, surpassing the primary endpoint criteria of 40%. Significant hematologic toxicities were observed, including grade 3 and 4 anemia (17%), thrombocytopenia (30%), neutropenia (50%), and febrile neutropenia (3%).[13] The results of a phase II study with a modified oral dose of 125 mg daily for 21 consecutive days in 28-day cycles (NCT01209598) were reported at the 2013 ASCO Annual Meeting, which indicated a comparable 12-week PFS but with reduced bone marrow toxicity.[14]

CDK4−LEE001 and LY2835219. Other CDK4 inhibitors are in clinical trials, including LEE001 and LY2835219. These agents exhibit a somewhat different toxicity profile, with neutropenia and QTc prolongation more common with LEE001 and gastrointestinal toxicity more common with LY2835219.[15,16] Stable disease was noted in patients with liposarcoma, although the complete results with these agents in this disease are pending publication.

One unresolved question is whether there exists a biomarker to predict clinical benefit. Rb expression appears to be necessary, but its presence is not predictive of benefit.

MDM2 targeting. Recently, it has been shown that CDK4 inhibition induces a G1 cell cycle arrest in all liposarcoma cells. However, only some of these cells undergo a process of cell death called cellular senescence. The proteolytic turnover of MDM2 appears critical for the induction of cellular senescence induced by palbociclib and by suppression of CDK4 by siRNA. Furthermore, the loss of MDM2 expression induced by CDK4 inhibition appears to be dependent on the baseline expression of ATRX. An examination of MDM2 loss in liposarcoma patients treated with palbociclib has been shown to correlate with prolonged stable disease; whereas patients with no change in MDM2 expression had rapid disease progression with this therapy. The importance of baseline ATRX expression, and the loss of MDM2 expression as a maker of clinical benefit to CDK4 inhibitors in liposarcoma (as well as other tumor types), will require validation in future clinical trials.[17]

MDM2 gene amplification or protein overexpression has been demonstrated in several cancer types, including DDLS.[18] Disruption of MDM2 and *p53* interaction in cancer types with wild-type *p53* and MDM2 overexpression has shown promise in vitro and in vivo. Nutlins are a class of imidazoline compounds that have been shown to have potent and selective activity against MDM2.[19] In preclinical studies, nutlin-3a was the first drug to show potent in vitro effects in liposarcoma cell lines with amplifications and overexpression of MDM2.[7] This drug induced both cell

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KEY POINTS

- Sarcomas are rare malignancies of mesenchymal origin that represent a heterogeneous group of over 50 subtypes, of which liposarcomas are one of the most common subtype.
- Liposarcomas contain at least four distinct subtypes for which treatment has to be tailored.
- Well-differentiated liposarcoma is the least malignant form, does not respond to chemotherapy, and tends to recur locally.
- Dedifferentiated liposarcoma has some response to chemotherapy and, like well-differentiated liposarcoma, contains amplification/overexpression of murine double minute 2 and cyclin-dependent kinase 4, inhibition of which have shown promise in early-phase clinical trials.
- Retrospective data indicate trabectedin to have activity in myxoid (round cell) liposarcoma, which is currently under U.S. Food and Drug Administration review for this indication.

FIGURE 1. Primary Liposarcoma Subtypes

Pleomorphic (5%)
High recurrence
Chemo-responsive

MRCL (30%)
Aggressive
FUS-DDITR
PIK3CA
Trabectedin
Chemo-sensitive

WDLS (40%)
Local recurrence
CDK4
MDM2
Chemo-resistant

DDLS (25%)
Distant recurrence
CDK4
MDM2
Chemo-insensitive
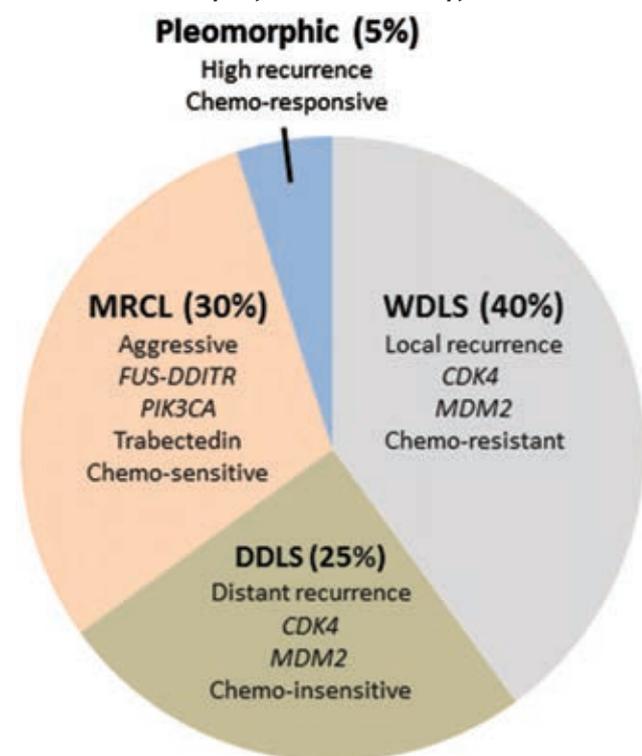
cycle arrest and apoptosis in these cells, which were also *p53* wild-type.[19]

MDM2−RG7112. RG7112 was the first nutlin inhibitor to be tested clinically. In a proof-of-concept study, 20 chemotherapy-naive patients with primary or relapsed WDLS (11 patients) or DDLS (9 patients) were enrolled in the neoadjuvant setting. Patients were treated with up to three cycles with 1,440 mg/m^2 of RG7112 for 10 days on a 28-day cycle schedule. Two of the 20 patients carried missense mutations in *TP53* and 14 of 17 had *MDM2* amplifications (three did not have adequate samples). Patients underwent paired biopsies before and on day 8 of treatment. *p21* expression, a marker of *p53* function, increased 3.48-fold in tumor tissue as measured by immunohistochemistry, while macrophage inhibitory cytokine-1 (MIC-1) levels, a marker of apoptosis and *p53* induction, increased in blood. *p53* expression and *MDM2* transcripts also increased by 4.86- and 3.03-fold compared to baseline, respectively. Nineteen patients received at least one cycle of RG7112, of which ten and five completed three and two cycles, respectively. One patient achieved a partial response, 14 had stable disease, and five experienced disease progression (all of whom had DDLS).[20] Ten patients underwent surgical resection at a median of 34.5 days after the last dose of RG7112, of which eight had a complete resection and two had partial resections.[20] Patients with partial resection received three cycles of adjuvant treatment and maintained stable disease.

Ten serious treatment-related adverse events (AEs) were observed in seven patients, all of which were hematologic in nature. Grade 3 or 4 AEs included neutropenia (30%), febrile neutropenia (5%), thrombocytopenia (15%), nausea (5%), emesis (10%), diarrhea (5%), and general deterioration (5%). One patient died of nontreatment-related postoperative hemorrhagic complications. Hematologic AEs, including thrombocytopenia, led to treatment delays in many patients; three had to discontinue treatment. All patients recovered from their hematologic AEs and there were no treatment-related bleeding complications.[20] RG7112 treatment in mice and monkeys also resulted in thrombocytopenia by promoting megakaryocyte progenitor cell destruction by apoptosis and inhibition of DNA synthesis during endomitosis, a key step for platelet production.[21]

MDM2−SAR405838. SAR405838 is an oral spirooxindole derivative antagonist that binds to MDM2 with a Ki of 0.88 nmol/L, has high specificity, and has a dissociation constant of 9.4 nmol/L. A cocrystal structure of SAR405838 and MDM2 indicates that SAR405838 mimics three key p53 amino acids and binds to the unstructured N-terminus of MDM2 to achieve high affinity.[22] SAR405838 activated wild-type *p53* function in vitro and in xenograft tumor tissue of solid tumors, leading to *p53*-dependent cell cycle arrest and/or apoptosis. SAR405838 resulted in transcriptional up-regulation of PUMA, a transcriptional target of p53, induction of apoptosis, and complete tumor regression in SJSA-1 osteosarcoma xenograft model.[22] A first-in-human phase I trial in patients with solid tumors evaluated once-daily and weekly schedules of SAR405838.[23] Only patients with DDLS were included in the maximum tolerated dose (MTD) expansion cohort. Sixty-eight patients were enrolled in the trial, of which 43% had liposarcoma. At the time of publication, 65 patients had discontinued study participation and three remained on study. Of the 65 patients, 47 discontinued participation because of disease progression, nine because of AEs, and nine for other reasons. Median duration of treatment was 42 days and MTD was established at 300 mg orally daily. Within the expansion cohort, 21 patients with DDLS were treated at 300 mg orally daily. The most common treatment-related AEs within this cohort included nausea (38%), fatigue (33%), diarrhea (24%), and thrombocytopenia (14%). Eight patients discontinued treatment because of AEs. Of note, no dose-limiting toxicities were observed on the weekly schedule of SAR405838.[23] Pharmacokinetic studies indicated a T_{max} of approximately 4 hours and half-life of nearly 16 hours. Plasma MIC-1 protein concentration correlated positively with SAR405838 exposure. Interestingly, a lower platelet count correlated with higher SAR405838 levels on a daily administered schedule, but a higher C_{max} achieved on the weekly schedule did not correlate with lower platelet counts. Overall, the best response was stable disease in 32 patients (47%), of which 13 patients (19.1%) had stable disease at 12 weeks. In the MTD expansion cohort with DDLS, 11 of 21 patients (52%) had stable disease as best response.[23]

MYXOID (ROUND CELL) LIPOSARCOMA

Myxoid (round cell) liposarcomas (MRCL) mostly arise in deep soft tissue of the extremities in patients who tend to be younger than those with other sarcoma subtypes. MRCL represents a single entity with variable round cell component and accounts for 30% to 35% of liposarcomas.[24] Round cell liposarcoma is considered a more aggressive subtype of myxoid liposarcoma, with greater than 5% round cell component carrying an unfavorable prognosis.[25,26] Unlike other tumors, MRCL tends to spread to serosal surfaces, bones, the abdominal cavity, and other soft tissues, even in the absence of lung disease.[27] Microscopic evaluation identifies tumors composed of uniform round-to-oval primitive nonmesenchymal cells and a variable number of monovacuolated lipoblasts. More than 90% of MRCL tumors contain the 12q13 and 16p11 translocation that leads to the *FUS-DDITR* (*TLS-CHOP*) fusion. Fused in sarcoma (FUS) protein, EWSR1, and TAF15 belong to the FET family of proteins and are involved in regulation of transcription and RNA splicing. DDIT3 is a leucine zipper containing transcription factor and is a member of the C/EBP family that plays a role in adipocyte differentiation and cell cycle control.[28] The fusion protein is thought to result in malignant transformation by favoring adipocyte differentiation over proliferation. These tumors are also characterized by mutations in *PIK3CA*, encoding the catalytic subunit of phosphatidylinositol 3-kinase (PI3K).[10] In a series of 71 patients with MRCL, 13 had point mutations in *PIK3CA*. These mutations were clustered in two domains, the helical domain (E542K and E545K) and the kinase domain (H1047L and H1047R). Interestingly, patients whose tumors harbored mutations in *PIK3CA* had a shorter duration of disease-specific survival than did those with wild-type *PIK3CA* (p = 0.036, log-rank test).[10]

Surgery alone or with radiation therapy is the mainstay of treatment, but despite appropriate treatment for local disease, nearly 40% of patients experience disease relapse.[29] Although MRCL is relatively more chemotherapy-sensitive compared to other STS, median survival is 2 years in the advanced disease setting.[30]

Trabectedin

Apart from chemotherapy, trabectedin (ET-743), a marine alkaloid, is approved in Europe as second-line treatment for advanced STS and is a promising agent, particularly in MRCL. Trabectedin has two known functions: 1) It binds to DNA within the minor grove of the double helix, causing a conformational change that likely changes its interactions with DNA-binding proteins, and 2) it causes double-stranded DNA breaks by interaction with transcription-coupled nucleotide excision repair complex. Owing to its ability to alter DNA–protein interaction, it is not surprising that trabectedin specifically inhibited type I and II *TLS-CHOP* transcripts from binding to their cognate target promoters in an MRCL xenograft model that impeded TLS-CHOP function.[31] Recent evidence has suggested that trabectedin also affects the tumor microenvironment by targeting monocytes and macrophages that have protumoral functions, including production of growth factors, neoangiogenesis, increased protease activity, and support in tumor cell dissemination.[32-35]

Fifty-one patients with advanced myxoid liposarcoma treated with trabectedin on a compassionate-use basis were analyzed retrospectively and found to have an overall response of 51%, including two patients who achieved a complete response. Median PFS was 14 months and PFS at 6 months was 88%.[24] In a single-center retrospective study of 21 patients treated with trabectedin for a median of four cycles, an objective partial response was achieved in three patients (14%) and eight patients (38%) achieved stable disease for a median duration of 4.5 months.[36] The benefit of trabectedin in other liposarcoma subtypes remains to be defined.

PLEOMORPHIC LIPOSARCOMA

Pleomorphic liposarcoma (PLS) represents approximately 5% to 15% of liposarcomas[37] and usually presents in adults within the lower extremity.[38] PLS pathologically exhibits large, multivacuolated pleomorphic lipoblasts.[39] PLS is associated with a poor prognosis, with high local recurrence and distant metastasis in the range of 30% to 35%.[40] Because of the rarity of the disease, treatment data within this particular subtype is limited. A retrospective study reviewed response to chemotherapy in 39 patients with unresectable or metastatic PLS.[41] Of the 32 patients assessable for response, one (3%) had a complete response, 11 (34.5%) had a partial response, and nine (28%) had stable disease, with a median follow-up of 62 months. The median PFS and OS were 4.3 and 14 months, respectively. The overall objective response rate was 37%. Interestingly, anthracycline-based regimens did not result in an improved response rate compared to nonanthracycline-based therapies.[41]

CHEMOTHERAPY AND LIPOSARCOMA SUBTYPE SENSITIVITY

Overall, liposarcomas do not respond well to systemic cytotoxic chemotherapy. The Royal Marsden study addressed the subtype-specific sensitivity to chemotherapy in a retrospective analysis of a prospectively maintained database of patients treated between August 1989 and June 2004. Of the 88 patients with liposarcoma treated, 94% of patients received first-line chemotherapy for metastatic disease or for local recurrence. Thirty percent received doxorubicin and 17% received ifosfamide as monotherapy, while 34% received the combination. Of the subtypes treated, the most response rates were observed in the myxoid subtype (48%), while PLS (33%), DDLS (25%), and round cell liposarcoma (17%) achieved some response, in contrast to WDLS which had none. Combination chemotherapy with doxorubicin and ifosfamide resulted in the greatest response rates across subtypes.

Another large retrospective study of 208 patients, which focused on patients with advanced WDLS and DDLS from 11 participating institutions, identified that 85 patients (41%)

received combination chemotherapy and 123 patients (59%) received single-agent chemotherapy.[43] The majority of patients (82%) received anthracycline-based therapy. Only 21 patients (12%) achieved an objective response, all of whom received anthracyclines. With a median follow-up of 28 months, median PFS and OS were 4.6 and 15.2 months, respectively. A trend toward a higher median PFS in WDLS (8.7 months) compared to DDLS (4 months) was noted. On multivariate analysis, age and performance status (PS) were the sole factors that independently associated with PFS, while grade and PS associated with OS.[43]

SUMMARY AND FUTURE DIRECTIONS

Although surgical resection remains the cornerstone for localized disease, treatment for unresectable or metastatic disease is highly dependent on the liposarcoma subtype. For patients with rapidly growing WDLS or DDLS, doxorubicin-based regimens can be considered as a treatment option, although response rates remain low. In contrast, for patients with MRCL, doxorubicin-based chemotherapy is the treatment of choice and trabectedin (where available) can also be considered as a treatment option. The role of *PIK3CA* inhibitors in this disease remains to be defined, but the opening of MATCH trials through the National Cancer Institute with agents targeting *PIK3CA* may soon answer this question. The importance of trabectedin and newer cytotoxic agents, such as eribulin in liposarcoma subtypes other than MRCL, continues to be defined. For PLS, chemotherapy remains the treatment of choice, although the prognosis in this setting is poor. Palbociclib, a CDK4/6 inhibitor, which was recently approved in combination with letrozole for patients with estrogen receptor (ER)–positive advanced breast cancer, is active in patients with WDLS/DDLS. With this agent, some patients achieve prolonged stable disease after disease progression on prior therapies. As no randomized trials are currently planned with this agent in WDLS/DDLS, and in the

absence of any other active agents, off-label use of this agent remains a consideration. It remains to be determined whether this agent will be added to National Comprehensive Cancer Network Drugs & Biologics Compendium now that it is approved for patients with ER-positive breast cancer. Although MDM2 inhibitors have been successful in stabilizing tumors in WDLS and DDLS, the hematologic side effects, especially thrombocytopenia, remain a major hurdle in drug development. The key to advancement of MDM2 inhibitors in the clinic is to balance efficacy with hematologic toxicity. This may be accomplished by optimizing scheduling such that efficacious pharmacokinetics are achieved without appreciable toxicity.

Although these subtype-specific treatments should be viewed as signs of progress in the treatment of patients with liposarcomas, key challenges remain. First, targeting MDM2 and CDK4 in patients with WDLS and DDLS generally does not result in responses, but rather in disease stabilization. Recent reports of proteolytic turnover of MDM2 protein in the setting of CDK4 inhibition and the role of ATRX in cellular senescence versus quiescence may shed more light on the key mechanisms involved in CDK4/6 inhibitor response. This may ultimately provide a means to identify which patients will respond best to this type of targeted therapy. Second, since both WDLS and DDLS contain MDM2 and CDK4 amplification/overexpression, these changes solely cannot explain the aggressiveness of DDLS. The molecular switch or switches that convert WDLS to DDLS require investigation. Third, the molecular pathways that drive this class of diseases, especially PLS, need to be further interrogated to identify actionable targets in these disease subtypes. Owing to their heterogeneity and diverse underlying molecular mechanisms that drive growth, it is not surprising that liposarcoma subtypes respond differently to distinct treatments. This genetic diversity provides unique opportunities in drug development and has provided patients with liposarcoma new hope in treatment of their disease.

Disclosures of Potential Conflicts of Interest

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TUMOR BIOLOGY

Implications of Intratumor Heterogeneity for Personalized Therapy

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Clonal Evolution Models of Tumor Heterogeneity

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OVERVIEW

Somatic/clonal evolution is the process of sequential acquisition of vertically transmittable genetic/epigenetic elements in multicellular organisms. Cancer is the result of somatic evolution. Understanding the processes that shape the evolution of individual tumors might help us to treat cancer more efficiently. The initiating genetic/epigenetic events occur in functional cells and provide the cell of origin a selective advantage under a changing environment. The initiating genetic events tend to be enriched in specific tissues (and are sometimes specific for those tissues), as different tissues undergo different changes in the environment that will activate selective forces on different cells of origin. For the initial clonal expansion to occur premalignant clones need to have a relative fitness advantage over their competitors. It is estimated that the premalignant phase can take several years. Once the premalignant clonal expansion is established, the premalignant cells will contribute to the changing environment and will start competing among themselves. In late stages of cancer evolution the environmental changes might be similar across different tissues, including a lack of physical space, a shortage of energy, and activation of the immune system, and more and more of the hallmarks of cancer will evolve. In this review we will explore the possible clinical relevance of the heterogeneity that evolves during this long somatic evolution. Above all, it should be stressed that the earlier the clonal expansion is recognized, the less diverse and less fit for survival the cells in the population are.

Cancer evolutionary biology is the study of the history of a tumor and the processes that have shaped its diversity. The major aim of this review is to build a meaningful link between evolutionary concepts and practical applications in cancer medicine. To eliminate all cancer cells without destroying the host (human or tissue) one should understand the branching processes that separated the cancerous clones from their normal cell of origin. Much like penicillin targeting a critical speciation event (the bacteria cell wall), an anticancer drug such as imatinib targets a critical event in the somatic evolution of myeloid progenitor survival.

Cancer evolutionary biology seeks to explain all the characteristics of a single tumor in a single individual; however, in this short review we will focus on the clinical relevance of tumor heterogeneity. As human cancers can evolve over many years with prolonged clinically latent periods,[1] relatively short generation times, ongoing mutation, and ever-changing environments, it is expected that the genotypic and phenotypic intratumor diversity will be substantial. However, key questions in cancer evolution need to be addressed before a clinician will be able to decide whether the treatment or diagnosis should be changed based on the presence of multiple sub-populations within a single tumor. For example, it is not clear in all cancers whether the ancestral clones of a tumor disappear (linear model) or whether several phenotypically distinct clones evolve in parallel (branching evolution).[1]

Regardless of the evolutionary model involved, the order of phenotype appearance is unclear. Another unresolved question in cancer evolutionary biology deals with the use of appropriate tools to describe intratumoral heterogeneity. Although the coding regions of the genomes of humans and chimpanzees are almost identical (99.4%) any child can tell the difference between the two species. Interestingly, RNA expression from different tissues demonstrates substantial differences between humans and chimpanzees (31.4% different).[2] Similarly, different clones from the same colon carcinoma showed phenotypically distinct behavior whereas the coding region sequence was almost identical.[3] Unlike germ-line evolution, somatic evolution (the driving force of cancer) can include a higher complexity of epigenetic transmittable information in the form of methylation, a chromatin modulation that can be stably vertically transmitted from cell to cell and defines unique phenotypes. Recent technologic advances in modern pathology have made it possible to analyze DNA, RNA, and protein from different portions of a single human tumor. Such an approach, combined with functional studies, kinetic assays, and the description of the environment that shapes evolution, hold promise for a better understanding of cancer mechanisms and their relevance to diagnosis, prognosis, and treatment.

SAMPLING ISSUES IN CANCER DIAGNOSIS

Accurate diagnosis is the first step in cancer therapy. In some cases, decisions regarding the most appropriate therapy are

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based on genetic testing of the tumor tissue and identification of specific targetable mutations. For example, studies in EGFR-mutant lung adenocarcinoma demonstrated a marked improvement in response rate, progression-free survival, and quality of life using EGFR tyrosine kinase inhibitors compared to chemotherapy, whereas in EGFR wild-type tumors the opposite was true.[4,5] With increasing evidence for intratumoral heterogeneity, one should wonder whether a small biopsy specimen actually represents the entire tumor mass. This issue was addressed in two recent studies that applied whole-exome or whole-genome sequencing to multiple regions of non-small cell lung cancer. Interestingly, the results of these studies were conflicting; one group identified known driver mutations in different samples of individual tumors, suggesting that sequencing of a single region well represents the tumor,[6] whereas the other group found regionally separated driver mutations, which obviously complicates targeted treatment selection.[1] Similar discrepancies in mutation status between primary tumors and metastases for common oncogenes have been described and reviewed.[7] For example, in a metastatic breast carcinoma the discordance in estrogen receptor, progesterone receptor, and HER2 receptor status between confirmed primary and recurrent breast cancer metastasis was 12.6%, 31.2%, and 5.5%, respectively.[8] Additionally, in lung adenocarcinoma the primary-metastasis discrepancy ranged from 0% to 34% for activating EGFR mutations in different series.[7] In colon carcinoma, despite some discordance in KRAS mutation status between adenomas and carcinomas,[9] there are very high concordance rates between primary tumor and metastasis,[10,11] indicating that, at least for colon carcinoma, the primary tumor and metastasis are equally suitable for diagnosis. In population genetics, different sampling approaches are used depending on the scientific question. Random sampling from limited locations (as used in most instances of cancer diagnosis) can underestimate population diversity if migration is low.[12] Direct sampling based on phenotypes can miss recent population expansions. Taking into account sampling issues and adapting knowledge from population genetics might lead to a better estimation of cancer diversity and its relevance to outcome.

KEY POINTS

- Cancer evolutionary biology aims to understand the processes shaping genotype–phenotype correlations in cancer.
- Cancer evolution is a long process, usually occurring over years, with a premalignant phase occurring in functioning cells.
- During evolution, heterogeneity is created not only at the DNA level.
- Early cancer events are tissue specific and can be used for targeted therapies; however, if diagnosed late they might be irrelevant to tumor survival.
- The earlier a cancer is diagnosed, the lower the tumor heterogeneity and the better the prognosis.

QUANTITATIVE CANCER GENETICS

Evolutionary biology is a quantitative methodology in which defined allele frequencies are monitored on a time scale. Current pathologic reports of cancer mutation analysis are in most instances binary and thus qualitative. For example, a patient harboring a "druggable" mutation in 5% of his/her tumor tissue would screen positive using sensitive testing modalities and would be treated with targeted therapy even though 95% of the tumor cells should respond better to classic chemotherapy. Overall, such a patient might benefit from a combination therapy. Incorporating quantitative genetic and epigenetic analysis to the decision-making algorithms of a clinical trial is a cumbersome task as the heterogeneity in the studied groups will increase; however, efforts should be made by oncologists to pursue such approaches.

EARLY AND LATE EVENTS IN CANCER EVOLUTION AND THEIR RELEVANCE TO TREATMENT

Cancer therapy approaches can be broadly divided into two categories: (1) treatments targeting general cancer mechanisms that are not tumor/tissue specific; such therapies are referred to as hallmark therapies.[13] (2) Treatments targeting tumor/tissue specific mechanisms/phenotypes that can be grouped under the umbrella of targeted therapies.

The hallmarks of cancer have evolved to increase the fitness of any cell in any tissue regardless of the environment or the cell of origin. Targeted therapies are often (but not always) tissue specific, and in most cases target mechanisms that have increased the fitness of a cell in a specific cell type or environment. It is important to realize that cancer is not a random process or a "bad cell" aiming to take over the tissue. Under the evolutionary theory, in any living system changes in allele frequencies and clonal expansions in populations are the result of a selective pressure introduced by the environment. There is a reason why most of the driver mutations described in cancers are somatic and not germ line: somatic mutations provide a selective advantage only to specific cells in a specific tissue under a specific environment that enabled their selection.

The early events in cancer evolution increase the fitness of a normal cell, as the very first mutation occurred in a functional cell that most probably expanded as a non cancerous functional cell with improved fitness[14,15] (reviewed by Shlush and Minden[16]). Therefore, it is predicted that early events will be tissue specific and therefore will be sensitive to targeted therapy. As the initiating cell gradually expands in an environment with limited resources, it is now the malignant cell population that introduces changes into the environment and in most tissues this will occur in a similar manner. Now, the selection will be for cells that are better able to replicate, migrate, and utilize energy, and the hallmarks of cancer will evolve together with increasing intratumoral heterogeneity (Fig. 1). For these reasons, the hallmarks of cancer are common to different tissues. Accordingly, the hallmarks of cancer can be later events in the evolution process and not shared

FIGURE 1. Tissue-specific Early Evolutionary Events versus Common Late Hallmarks of Cancer Events
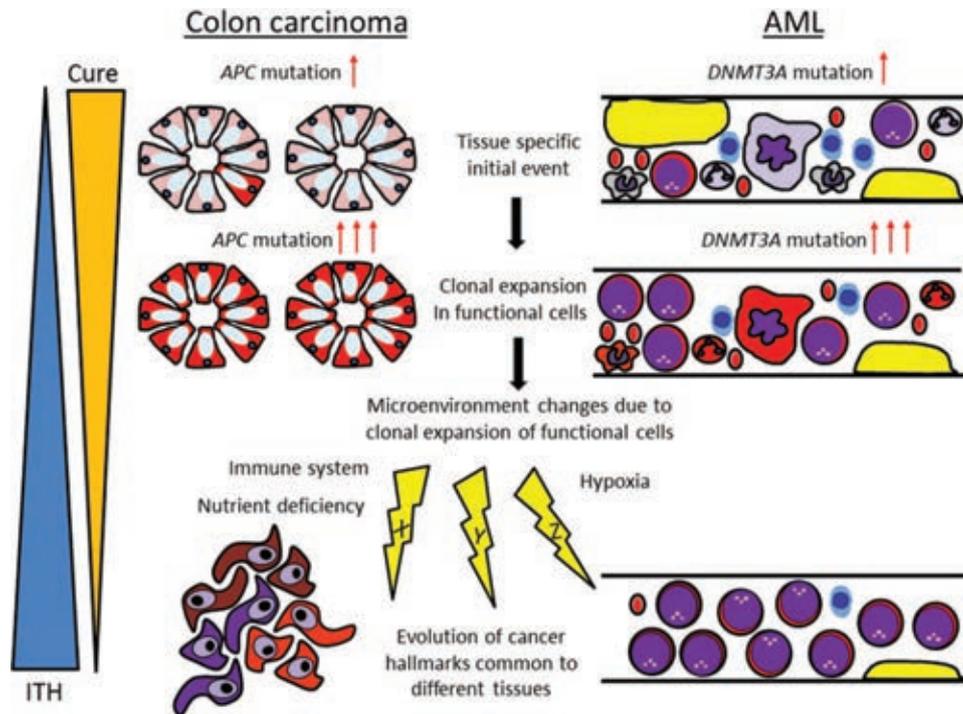
Early mutations are tissue specific and increase the fitness of the cell of origin under a changing environment. Initial clonal expansion of functional cells will eventually lead to changes in the environment that will in turn lead to selective pressure for the various hallmarks of cancer. Mutations (X,Y,Z) that have accumulated in the premalignant clones will be selected and gradually reduce the functionality of the cell of origin.

Abbreviations: AML, acute myeloid leukemia; ITH, intratumoral heterogeneity.

by all of the tumor cells. Unfortunately, it is not necessarily sufficient to target the tissue-specific phenotypes, because at the time of diagnosis (usually late in the evolution process) they might be unnecessary for survival. On a practical level, oncologists need to know what the major evolutionary events are in their tumor of interest, and in what order they occurred. This knowledge can be used in the planning of clinical trials and combination therapies. It is important to understand that a tumor presenting with the hallmarks of cancer has most probably evolved over a long period and might have lost some of the initial phenotypes that subsequently became superfluous for survival. Many cancers are diagnosed late in their evolution and if identified earlier they might have been targetable through their tissue-specific genotype/phenotypes.

INTRATUMORAL GENETIC HETEROGENEITY AND CANCER PROGNOSIS

Intratumoral heterogeneity has been demonstrated to be a predictive marker for cancer mortality. In Barrett's esophagus, the higher the diversity in a single biopsy the worse the prognosis.[17] Heterogeneity in HER2 amplification is associated with a higher cancer-specific death rate.[18] Similar findings were noted in breast carcinoma.[19] In head and neck cancer, intratumoral heterogeneity at the whole genomic level was significantly associated with shorter survival.[20] Additionally, the presence of sub-clonal driver mutations was

associated with reduced survival in chronic lymphocytic leukemia,[21] and patients with localized resected lung carcinoma that had a higher fraction of sub-clonal mutations were more likely to relapse.[6] These recent findings suggest that the degree of sub-clonality might serve as a cancer marker per se. Higher diversity is related to a higher mutation rate or longer tumor evolution with more replications. However, as discussed above, the survival of multiple clones suggests that multiple phenotypes were selected under different environments (branched evolution), all of which tell us something about the tumor biology and history.

FUTURE DIRECTIONS

The study of evolution, like the study of history, involves looking at the past to create a better future. Recent studies[14,15] suggest that early mutations in leukemia occur in cells capable of mainlining their functionality. These early events lead to clonal expansion of cells trying to maintain function. Clonal expansion is relatively common in the general population.[22-24] The early clonal expansion, which can last for years, will eventually progress to uncontrolled cell growth and the emergence of dysfunctional cells. From these studies we learn that cancer in adults is a longstanding state, with precancerous lesions most likely evolving as a result of the aging environment. Accordingly, we suggest that changing the environment and targeting early events might change the evolutionary trajectory of cancer.

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Relationships are considered self-held and compensated unless otherwise noted. Relationships marked "L" indicate leadership positions. Relationships marked "I" are those held by an immediate family member; those marked "B" are held by the author and an immediate family member. Institutional relationships are marked "Inst." Relationships marked "U" are uncompensated.

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TUMOR BIOLOGY

New Strategies to Understand and Target Initiation of Aggressive Cancers

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"Lassie," "Toto," and Fellow Pet Dogs: Poised to Lead the Way for Advances in Cancer Prevention

Deborah W. Knapp, DVM, Deepika Dhawan, PhD, and Elaine Ostrander, PhD

OVERVIEW

Cancer causes substantial morbidity and takes the lives of over 8 million people worldwide each year. Advances in cancer prevention research are crucial, and animal models are key to this. There are many valuable experimentally induced cancer models, but these do not fully meet the needs for cancer prevention studies. Pet dogs with risks for naturally occurring cancer can fill important gaps in cancer prevention research. Using invasive urothelial carcinoma (iUC) as an example, the advantages of utilizing pet dogs include: (1) close similarities between dogs and humans in carcinogenesis, molecular and cellular features, invasive and metastatic behavior, and response to treatment, thus providing high relevance for comparative studies, (2) shared environment between dogs and humans to help identify not-yet-known environmental iUC risks, (3) strong breed-associated risk (5- to 21-fold increased risk compared with mixed breeds) that facilitates investigation of gene-environment interactions, screening, and early intervention, (4) large size of dogs (versus rodents) that allows collection of fluids and tissues via cystoscopy, and detailed imaging at multiple time points, and (5) acceptance for studies in which each participating dog can benefit while enjoying life in their family environment, and in which findings will help other dogs and humans. An ongoing 3-year study in Scottish Terriers (comparable to a 15- to 20-year study in humans) is aimed at defining genetic and environmental risk factors for iUC, effective methods for screening/early detection, and a successful secondary cancer prevention approach with very promising results to date. Pet dogs can indeed propel cancer prevention research.

There is a need for improved cancer prevention research. More than 580,000 people in the United States and over 8 million people worldwide are expected to die from cancer, including all cancer types, yearly.[1,2] Although it is accepted that cancer prevention should offer the most cost-effective and appealing long-term strategy to control cancer, cancer prevention research has not kept up with the need, especially for an aging population.[3] One of the challenges in cancer prevention research is the identification and use of relevant animal models in which findings in the model will actually translate into improved prevention and treatment strategies for humans. Unfortunately, many preclinical models fail to reflect the disease in humans.[4-7] Other published concerns with experimentally induced models include: (1) the induction of cancer in animals that are young and otherwise healthy, whereas humans with cancer are often older with comorbid conditions, (2) the assessment of response in animals with homogeneous tumors versus that in humans with heterogeneous cancer, (3) timing of an intervention in animals that is unrealistic in humans, and (4) the use of toxic doses of treatment agents to achieve a desired outcome in animals when these doses would not be tolerated by humans.[6]

CANCER PREVENTION RESEARCH AND THE VALUE OF PET DOGS
Strong Potential Value for Pet Dogs in Cancer Research

There is growing evidence that pet dogs with specific forms of naturally occurring cancer can serve as highly relevant models for those cancers in humans.[8-12] There are an estimated 83 million pet dogs in the United States,[13] and a quarter of older pet dogs are expected to die from cancer.[8-12] For specific types of naturally occurring cancer, including, but not limited to, invasive urinary bladder cancer,[8] osteosarcoma,[14] subsets of squamous cell carcinoma,[9] and lymphoma,[15,16] considerable similarities have been noted between the cancer in dogs and humans in regards to histopathology, molecular features, and biologic behavior. Importantly, these cancers develop in the context of an intact immune system, and are characterized by considerable heterogeneity within and between individuals, similar to human cancer.[10] Studies to date indicate that the genes and pathways involved in cancer development in dogs are similar to those in humans.[17,18] Dogs develop cancer in an environment shared with their owners, and this has enabled dogs to serve as sentinels for specific carcinogens such as asbestos exposure and mesothelioma risk.[19] Studies

in dogs can help identify not yet known exposures that have the potential to contribute to understanding of human cancer.[20-22] The compressed life span of dogs compared with humans facilitates cancer prevention research in that a 15 to 20 year period in human life can be studied in dogs in 2 to 3 years. In an intriguing example, a 7-month study in older dogs (physiologically equivalent to human age 62 to 69) demonstrated a U-shaped dose-response relationship between selenium status (toenail selenium concentration) and provided target concentrations to prevent DNA damage and induce apoptosis within the prostate.[23-24] Midrange concentrations were associated with protective effects, whereas DNA damage was most pronounced at the lowest and highest selenium concentrations along the curve. This study offered a possible explanation for the failure of the 7-year Selenium and Vitamin E Cancer Prevention Trial (SELECT) of 35,000 men, which had begun before the dog study; the concentrations achieved in men in the SELECT study were not in the beneficial range as defined by the dog study.

Study Opportunities Afforded by Strong Breed-Associated Risk for Cancer in Dogs

Another intriguing aspect of cancer research in pet dogs is the tremendous opportunities offered by strong breed-associated risk for certain types of cancer. Examples include the 23-fold increased risk for squamous cell carcinoma of the digit in Giant Schnauzers[9] and the 21-fold increased risk for invasive bladder cancer in Scottish Terriers[8] compared with mixed breed dogs. These findings, along with the sequencing of the dog genome,[25] offer unparalleled opportunities to uncover complex traits leading to cancer development, including gene-gene and gene-environment analyses. For a specific cancer type, the number of deleterious alleles segregating in a single dog breed is expected to be limited because of essentially closed breeding in the establishment and maintenance of the breed.[9] Dog breeds are genetically far more simple compared with dog or human populations as a whole.[26] This

allows researchers to circumvent small family size, outbred population structure, and locus heterogeneity that limit human cancer gene mapping.[27,28] Detailed records of dog breeding by breed clubs add to the value of the model.[9] When taking advantage of breed-associated cancer risk, including genome wide association studies (GWAS), analyses can be performed with much fewer subjects than would be required for a human GWAS study. For example, an initial GWAS performed on 31 Standard Poodle cases and 34 controls allowed identification of a locus on canine chromosome 15 for squamous cell carcinoma of the digit with high significance that spanned approximately 1 million base pairs. Additional mapping and sequencing with less than 100 additional dogs revealed a founder mutation—a copy number variant affecting *KITL* expression.[9,29] The expectation is that there are shared genetic factors that drive cancer development in both dogs and humans; however, many of these factors are difficult to elucidate in humans, but dog studies can allow the identification and understanding of complex traits important in human cancer.

One example of this involves mutations leading to a renal cancer syndrome in German Shepherd Dogs that mimics that in Birt-Hogg-Dubé syndrome in people.[30] The locus was initially found using one large family, characterized by a single male that had been crossed to a number of females. Analysis of the progeny of the crosses allowed the locus to be reduced to a small size, and the underlying causative gene, folliculin, to be identified. Of note, the locus was mapped first in dogs, then in humans. Yet mutations in the same gene produce very similar cancer syndromes in humans and dogs.

NEEDS AND OPPORTUNITIES IN INVASIVE BLADDER CANCER RESEARCH
Current Challenges in Human Invasive Bladder Cancer
One of the best examples of a canine cancer with high translational potential and value is invasive urinary bladder cancer, specifically iUC, also referred to as invasive transitional cell carcinoma. There is a clear need to improve the outlook for people who have or who are at risk for developing this cancer. More than 16,000 people in the United States[31] and over 160,000 people worldwide[32] die from iUC each year. Clinical consequences include urinary obstruction as a result of progression of the primary tumor and major organ failure from metastasis. Both can cause substantial morbidity and lead to death. The mainstay of front-line treatment for bladder-confined iUC is cystectomy.[33] Many patients, however, are not candidates for this involved surgery because of comorbid conditions. Of those who undergo surgery, approximately 50% develop distant metastases.[34] Despite initial favorable response to chemotherapy, drug resistance develops in almost all patients with metastases, ultimately leading to death. The median survival time for patients with metastatic disease (approximately 14 months) has not improved to any extent in more than 20 years.[35] In addition, there is a huge economic burden associated with bladder cancer. Lifetime health care costs for patients with muscle invasive blad-

der cancer are estimated to average $150,000 per patient.[36] In the United States alone, $4 billion is spent on the medical costs of bladder cancer (including all forms of the cancer), and the lost life costs are estimated at $17 billion per year from premature death from bladder cancer.[36] There is a clear need to develop and implement strategies to prevent the development and progression of iUC.

To make progress against iUC, research involving animal models is crucial. Experimentally induced models of bladder neoplasia include chemically induced tumors, transgenic mouse models, and orthotopic xenograft models.[37,38] Although these experimental animal models are informative and are extensively used in bladder cancer research, there is still a need for complementary animal models in which the cancer is naturally occurring, invades and metastasizes consistently, and more closely mimics iUC in humans. Pet dogs with naturally occurring invasive iUC provide an ideal animal model to address this need.[8]

Pet Dogs Contributing to Invasive Bladder Cancer Research

Bladder cancer makes up 2% of all naturally occurring cancers in dogs, similar to the frequency in humans.[39,40] By conservative estimates, iUC occurs in at least 20,000 pet dogs per year, although the cancer in many of these dogs goes undiagnosed.[39] Most dogs with bladder cancer have high grade iUC, with superficial low grade tumors being rare in dogs.[8,41] There are marked similarities between the histopathology of iUC in dogs and humans, and reported cellular and molecular features are also similar across the two species.[8] Gene expression array analyses also demonstrate considerable similarities between iUC in dogs and humans (D. Dhawan, D.W. Knapp, C. Khanna, unpublished data 2015).

The locally invasive and metastatic behavior of iUC in dogs mimics that in humans. Nodal and distant metastasis are common, with up to 20% of dogs having metastases at diagnosis and 67% having metastases at death including distant metastases confirmed at necropsy in almost 60% of dogs.[8] Common distant sites of metastasis include lung, liver, and bone.[8]

Invasive UC is typically a disease of older dogs with median ages at diagnosis ranging from 9 to 11. In contrast to iUC in humans, female dogs have a higher risk of the cancer than male dogs (female-male ratios 1.7:1 to 1.9:1), and interestingly, neutered dogs have a higher risk than sexually intact dogs.[8] Hematuria and stranguria are the most common presenting signs. Cystectomy is rarely performed in pet dogs because of the expense and morbidity, and the frequent extension of the cancer down the urethra.[8] Radiation therapy is infrequently applied, and the mainstay for treatment of iUC in dogs is chemotherapy, cyclooxygenase inhibitors, and combinations of these. Platinum agents appear to be the most active, especially when combined with a cyclooxygenase inhibitor, which substantially enhances the activity of the platinums.[8] Medical therapy can allow excellent quality of life in most dogs for several months to over a year, but unfortu-

nately the development of drug resistance is common and most dogs ultimately die from the cancer.

There are multiple ongoing clinical trials for pet dogs with iUC. Similar to human studies, the pet dogs live at home, and come into the Veterinary Teaching Hospital periodically for evaluation. Canine trials are performed with institutional approval and informed pet owner consent. Clinical trials are well accepted as a win-win-win scenario in pet dogs with iUC. Each participating dog is expected to benefit as they gain access to a promising new treatment that is expected to be well tolerated and that is usually less expensive than other treatments. Additionally, crucial new knowledge is gained, which can improve the outlook for other dogs and, ultimately, for humans with the cancer.[8] In fact, at the Purdue University College of Veterinary Medicine, where two of the authors (Knapp and Dhawan) are employed, more than 90% of owners of dogs with iUC elect to enroll their pet in a clinical trial. Parallel mechanism studies are feasible in dogs with samples of blood, urine, and in some cases tumor tissues collected via cystoscopy before and during therapy. Most pet owners will also allow a necropsy of the dog when it dies or is euthanized (as a result of declining quality of life from cancer that progression or other conditions). Treatment trials in dogs that have been translated, or are poised to be translated because of the success in dogs and applicability to humans, include cyclooxygenase inhibitor treatment, folate-targeted therapy, and demethylating treatments.[8,42,43]

Not only can dogs with iUC facilitate the development of better treatment, dogs at risk for iUC may hold equal or more value in cancer prevention research. Understanding the causes of a particular type of cancer would undoubtedly aid in the development of prevention strategies. The greatest risk factor for iUC in humans is exposure to cigarette smoke. Exposure to other chemicals also increases risk, but 50% of patients with iUC have no known risk factors for the cancer. Although cigarette exposure has not yet been linked to iUC risk in dogs, other chemicals can have a profound effect on cancer risk. Exposure to older generation flea control products, which in some instances contained benzene and toluene (known carcinogens in humans), resulted in more than a 20-fold increased risk in iUC in dogs across many breeds, especially in female and obese dogs (other risk factors). In Scottish Terriers, who have a strong breed-associated risk for iUC, exposure to lawn chemicals resulted in an additional 7-fold increased risk compared with that in unexposed dogs. A follow-up study revealed widespread uptake of lawn chemicals into the urine of dogs exposed to treated lawns and untreated lawns contaminated by chemical drift. Some, but not all, studies suggest a link between exposure to herbicides, pesticides, and contaminants in agricultural chemical mixtures and iUC risk in humans.[44-46] In humans, genetic factors, especially in relation to chemical exposures, are associated with increased iUC risk, although the understanding of these gene-environment interactions is limited.[47-49] Studies are needed to further identify these factors and gene-environment interactions that increase iUC risk, and dog studies could prove crucial in this regard.

TABLE 1. Breed-Associated Risk for iUC in Dogs Identified in Analyses of Veterinary Medical Data Base Records

Breed	OR Compared with Mixed Breed	95% CI
Mixed Breed Dog (Reference Category)	1.0	NA
Scottish Terrier	21.12	16.23-27.49
Eskimo Dog	6.58	3.34-12.96
Shetland Sheepdog	6.05	4.76-7.69
West Highland White Terrier	5.84	4.23-8.08
Keeshond	4.26	2.25-8.07
Samoyed	3.43	1.81-6.49
Beagle	3.09	2.34-4.08

Abbreviations: OR, odds ratio; NA, not applicable.
Records from Participating Veterinary Colleges in the United States and Canada of dogs with iUC and dogs in the same breed without iUC (SNOMED search, 1999-2010).

One of the most powerful aspects of the naturally occurring dog model for iUC is the strong breed-associated risk for the cancer in dogs. There are at least seven breeds of dogs in which the risks of iUC is over 3 times that of mixed breed dogs, with the most impressive risk being in Scottish Terriers (odds ratio [OR] 21.1; 95% CI, 16.23 to 27.49; Table 1). GWAS have been used to identify two loci with strong significance for iUC risk in dogs, and steps to elucidate the specific genes involved are underway (E. Ostrander, H.G. Parker, D.W. Knapp, unpublished data 2015).

The strong breed-associated risk can be used to select groups of dogs for the study of iUC screening, early detection, and early intervention. A study is underway in Scottish Terriers in which a minimum of 100 dogs over the age of 7 who have no current evidence of bladder disease and no history of bladder cancer will be monitored for at least 3 years. The study calls for evaluation at 6-month intervals with medical history, physical exam, ultrasound exam of the urinary tract, urine sediment exam, and multiple emerging urine-based assays to detect iUC. The goals of the study are to determine the percentage of dogs in which cancer or precancer (urothelial dysplasia, carcinoma in situ, and early-stage iUC) can be found before the onset of any clinical signs of disease, and to determine the appropriate screening interval, screening test, and age to begin screening. Dogs with evidence of cancer or precancer will undergo cystoscopy and biopsy. Those with precancer or early-stage cancer will be eligible to enroll in a secondary cancer prevention trial, with secondary prevention being an intervention implemented at the early-stage of cancer development to cause regression or to prevent progression. In this particular study, the secondary prevention agent being evaluated is a cyclooxygenase inhibiting drug. With the compressed aging in dogs, this 3-year study in dogs would be expected to be equivalent to an approximately 20-year study in humans. The expectation was that over a period of 3 years, precancer or cancer would be found in approximately 30% of the dogs. With the study still in its first year, however, the frequency of precancer and cancer detec-

tion is much higher than expected at this time point. And, with the cancer being found early, the antitumor effects of the cyclooxygenase inhibitor are also exceeding that typically observed in more advanced disease. It is anticipated that the treatment response with nontargeted approaches such as cyclooxygenase inhibitors, and to perhaps a greater extent with targeted agents, will be better in early cancer that has not acquired as many genetic changes leading to drug resistance. This is encouraging evidence that this approach is one that can be used to test current and future strategies for detection and early intervention of iUC. It is exciting to consider that dog studies, which are much quicker and much less expensive to perform compared with human studies, could be used to help design the approach with the highest likelihood of success for the lengthier and far more costly human trials.

CHALLENGES TO ADVANCING CANCER RESEARCH IN PET DOGS

Although there is substantial evidence for the value of pet dog studies in cancer prevention and treatment research that could positively effect human patients with cancer, there are challenges that need to be met to make the most use of this approach. There are at least three main areas where challenges must be met: (1) funding, (2) critical mass of veterinary scientists doing translational research, and (3) access to appropriate numbers of dogs for clinical studies. Regarding clinical research costs, dog trials are far less expensive than human trials. For example, an appropriately powered, randomized three-arm treatment trial in dogs, depending on the intervention being tested and numbers of dogs needed, could cost $1 million, whereas a similar study in humans would cost $10s of millions to over $100 million. Thus, one could clearly argue that if the dog study yielded results that were then used to markedly increase the odds of success in the human trial, that the dog study would be a very sound financial investment. All too often, however, when funding agencies and industry see that in some instances an entire mouse study could be done for the costs of one to two of the dogs in a trial, then the funding decisions go to the more traditional rodent experiments rather than the dog study. Part of this is because there has not been a "walk-off home run" in comparative oncology research in the last 20 years, in which the dog study was done first and the results clearly informed the design of a follow-up human study that was successful because of the dog work. There are numerous areas where translational researchers are on the brink for work that should have this high level of effect, but until that happens, funding agencies continue to opt for more traditional animal studies, even if those studies lack relevance to the human condition. Without funding for dog studies, however, the "walk-off home run" study is difficult, if not impossible, to achieve.

Another essential component of valuable translational research utilizing pet dogs is the scientists that will drive the work. The number of veterinary scientists with the knowledge, experience, translational mindset, willingness to conduct prospective clinical trials, and that make comparative

oncology research a main emphasis of their career is very limited. A unique set of skills and capabilities is needed, including knowledge of veterinary oncology, the human cancer focused in the research, and basic science that can be applied to improve the clinical condition, as well as excellent communication and people skills to build multidisciplinary teams (DVM, MD, PhD) to develop and accomplish the work, writing skills for successful grants and manuscripts, and the passion and drive to make the work happen. Forward thinking institutions are also key. Institutions need to build infrastructure and support, and allow individual faculty that have high potential to be the "research engines" to move away from the typical "triple-threat" position (equal time spent on clinical service, teaching, and research) of an academic veterinary oncologist. Some of the more successful veterinarians that have worked in translation research have spent time at a medical school or have had MD mentors. This enables them to better understand the most critical needs in human oncology and to network for collaborative research. The veterinary scientists must also have sufficient understanding of basic science to know how it could be applied to answer key clinical questions and to communicate with basic scientists for successful collaborations. Even with these skills and talents though, valuable translational research is going to require multidisciplinary teams.

Access to adequate numbers of dogs for clinical studies is obviously important. Currently, there is marked underutilization of dogs for clinical studies. In iUC for example, of the estimated 20,000 dogs that develop this cancer yearly, less than 5% of those dogs enter prospective clinical trials each year. There are programs in place, however, to accomplish canine clinical trials in which the numbers needed exceed that of a single institution. The best example is the Comparative Oncology Trials Consortium implemented by the Comparative Oncology Program at the National Cancer Institute.[50] This consortium includes academic veterinary oncologists at 20 veterinary colleges across the United States and Canada. Another consortium, the Canine Comparative Oncology Genomics Consortium (CCOGC)[50] sponsored by the National Cancer Institute, the American Kennel Club Canine Health Foundation, the Morris Animal Foundation, and Pfizer, is facilitating access to tumor and normal tissues and other samples from dogs through a biospecimen repository. Although this is an excellent starting point, this or similar repositories will need to expand to meet research needs in academia, nonprofit organizations, and industry/pharmaceutical companies, and to offer the possibility of a canine version of The Cancer Genome Atlas.[51]

In summary, clinical studies of pet dogs who have naturally occurring cancer or who are at risk for developing naturally occurring cancer can provide an unparalleled opportunity to make progress that will benefit humans, as well as pet dogs. Fortunately, there are solutions to overcome the challenges summarized above. This will allow pet dogs such as Lassie to "save the day" again, this time for cancer research!

Disclosures of Potential Conflicts of Interest

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TUMOR BIOLOGY

Targeting Cancer Metabolism

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Metabolism and Oxidative Stress Response Pathways in Kidney Cancer: A Tale of Chance and Necessity

Carole Sourbier, PhD, Ramaprasad Srinivasan, MD, PhD, and W. Marston Linehan, MD

OVERVIEW

Over 270,000 patients are affected with kidney cancer worldwide and 120,000 died from this disease in 2014. Over the last few decades, important progress has been made in our understanding of the genetic and molecular mechanisms underlying the growth of these tumors, which has led to improvement in patient care. Some of the most significant recent advances came from the increasing number of large datasets generated by bioinformatics (genomics, proteomics, etc.) and their integration to characterize the genetic and molecular factors responsible for kidney tumor development and survival. Interestingly, deregulated metabolism and oxidative stress pathways are commonly found in advanced-stage kidney tumors and are important factors to consider and potentially target when developing therapeutic approaches.

Patients with small and localized kidney tumors (known as renal cell carcinoma;RCC) who are treated with surgical resection or surveillance have a very high 5- and 10-year survival rate (over 95%). However, less than 15% of patients with advanced disease (T4 or M1) will survive longer than 5 years.[1,2] RCC is not a single disease; it is made up of a number of different types of cancer that occur in the kidney. Each type is characterized by different histology, a distinctive clinical course, disparate genetic changes, and requires distinct clinical approaches. The most common type of RCC is clear cell renal cell carcinoma (ccRCC). ccRCC represents 75% of all RCC and is characterized in 90% of cases by mutation of the *von Hippel-Lindau (VHL)* gene.[3,4] The second most common type of RCC is papillary RCC, representing approximately 15% of cases. Papillary tumors can be subcategorized into two distinct histologic subtypes: papillary type I and papillary type II. Papillary type I includes tumors with *MET* mutations and chromosome-7 amplification. Papillary type II, a heterogeneous group of tumors, includes tumors with tricarboxylic acid cycle (TCA) enzyme mutations, such as *fumarate hydratase* (*FH*), leading to a highly aerobic glycolytic phenotype and upregulation of the Nrf2-antioxidant response pathway. There are few therapeutic strategies specifically tailored to papillary tumors, and agents commonly used in ccRCC have only limited effectiveness in advanced papillary RCC.

It is known that dysregulation of cellular energetics and a metabolic shift to aerobic glycolysis is a hallmark of many types of cancer.[5-7] Initially described by Otto Warburg in 1924, cancers characterized by aerobic glycolysis undergo a metabolic shift to increased glycolysis despite the presence of oxygen and functioning mitochondria. Currently recognized as one of the "12 hallmarks of cancer,"[7] dysregulation of cellular energetic needs is supported by multiple genetic and molecular events. Some examples include the activation of the phosphatidylinositol-3 kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway or the VHL/hypoxia-inducible factor (HIF) pathway, which would affect different aspects of cellular metabolism and also the activation of "coping" pathways, such as the Nrf2 pathway, which allows cells to survive the oxidative stress linked with an aberrant metabolism.[8] Regardless of whether metabolic alterations of tumor cells are an initiating event leading to tumorigenesis or are an adaptation associated with an aggressive phenotype, identifying the metabolic events associated with RCC survival is an important step toward the development of effective forms of therapy for this group of tumors.

CLEAR CELL RENAL CELL CARCINOMA TUMORS
Targeting the VHL/HIF Pathway
Current therapies for patients affected with advanced ccRCC mostly target the VHL/HIF pathway. The VHL protein binds other proteins, such as elongin B, elongin C, and CUL2, to target the HIF for ubiquitin-mediated degradation. This is an oxygen-sensing mechanism.[9-11] The VHL complex targets hydroxylated proteins, such as the HIF1-alpha and HIF2-alpha, for proteasomal degradation. In normoxic conditions, HIF prolyl hydroxylase hydroxylates two proline res-

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idues on HIF-alpha. Under hypoxia, HIF is not hydroxylated, is not recognized by the VHL complex, and is stabilized. HIF1-alpha and HIF2-alpha are transcription factors that have downstream targets that are important for cell survival under hypoxic conditions and that regulate multiple biologic functions such as angiogenesis, energy metabolism, cell proliferation, erythropoiesis, and iron metabolism. Transforming growth factor alpha, vascular endothelial growth factor and its receptor, as well as the glucose transporters GLUT1 and GLUT4, and lactate dehydrogenase A (LDHA) are among HIF's downstream transcriptional targets. Since the identification of *VHL* gene mutations in ccRCC and elucidation of the role played by VHL in regulating the HIF pathway, numerous therapeutic approaches targeting this pathway have been developed.[10,12] However, although response rates can be substantial (in some cases as high as 40%), most disease eventually become resistant to therapy and progress. It has been shown in preclinical studies that HIF2-alpha is a critical pathway in VHL-deficient tumors.[13-15] Several strategies to inhibit HIF2-alpha have shown promising results in vitro in VHL-deficient tumor cell lines, and further studies are being conducted to facilitate evaluating this strategy in the clinic.[16-18] To improve the current clinical outcomes for patients with advanced ccRCC, development of more selective and potent agents targeting the vasculature might be necessary as well as a better understanding of how and why tumor cells are becoming resistant.

## UNDERSTANDING THE METABOLIC ADAPTATION OF CLEAR CELL RENAL CELL CARCINOMA TUMORS

Deciphering the molecular basis of ccRCC is critical for the development of effective targeted therapies. In report on ccRCC by The Cancer Genome Atlas, 19 substantially mutated genes were identified, including *VHL*, chromatin remodeling genes (*PBRM1, SETD2*, and *BAP1*), genes of the

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KEY POINTS

- Genetic and molecular mechanisms underlying renal cell carcinomas' developments drive metabolic changes in tumor cells.
- Advanced clear cell RCC and hereditary leiomyomatosis and RCC tumors share a similar metabolic profile consisting of a shift to aerobic glycolysis, enhanced glutamine metabolism, and increased fatty acid synthesis.
- Improvement in outcomes for patients with clear cell RCC has been made over the last 10 years by strategically targeting the VHL/HIF pathway.
- Targeting metabolic changes supporting tumor cells' survival might have a therapeutic value for clear cell RCC and papillary tumors.
- Imbalances in redox status are symptomatic of aggressive tumors and should be considered when developing a targeted therapeutic approach for RCC.

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PI3K/Akt pathway (*PTEN, PI3KCA*), the mTOR pathway (*MTOR*), and *P53*. By integrating genomic, proteomic, and transcriptomic data, this study reported findings in high-grade, high-stage ccRCC that were consistent with a metabolic shift toward aerobic glycolysis and decreased oxidative phosphorylation. These data provide the basis for the development of additional therapeutic approaches in patients with advanced ccRCC.

Over the last few decades, signaling pathways, such as PI3k/Akt/mTOR, AMPK, or PKC-theta, have been shown to be promising therapeutic targets for ccRCC in clinical or preclinical studies.[19-22] Many of these signaling pathways are implicated directly or indirectly in regulating cell metabolism (Fig. 1). For example, two agents targeting mTOR, a key node in cell metabolism, have been approved for the treatment of ccRCC (everolimus and temsirolimus).[23] mTOR is a serine/threonine protein kinase that interacts with several proteins to form two distinct mTOR complexes (mTORC1 and mTOCR2) that have different metabolic and biologic functions, different regulators, but share the same catalytic mTOR subunit (for review see Laplante M and Sabatini DM).[24] mTORC1 stimulates glucose metabolism and fatty acid synthesis via regulation of HIF1-alpha and SREBP1/2 activation respectively, while inhibiting autophagy and supporting macromolecule biosynthesis. mTORC2 activates Akt and supports cell survival and cytoskeleton dynamics.[24] It is thought that resistance to mTOR inhibitors such as rapamycin is at least partly due to the fact that rapamycin only inhibits mTORC1, and mTORC2 is able to overcome this inhibition by phosphorylating and activating Akt (and glucose uptake). Thus, novel mTOR inhibitors targeting the catalytic subunit (i.e., dual TORC1/2 inhibitors) as well as approaches combining PI3K/Akt inhibitors with mTORC1 inhibitors and dual PI3K/mTOR inhibitors are being developed. The PI3K/Akt signaling pathway is involved in the insulin response pathway and promotes glucose uptake via regulation of GLUT1/4.[25] Identified about 9 years ago as aberrantly activated in ccRCC and a potent preclinical therapeutic target,[19,20] it was shown to be associated with ccRCC tumor progression, partially because of its role in supporting glycolysis.[26] Several agents targeting the PI3K/Akt pathway are currently in development for ccRCC. Studies are underway to determine if targeting glucose uptake combined with inhibition of glutamine metabolism might be therapeutically beneficial in ccRCC. Since both glucose metabolism and reductive glutamine metabolism have been shown to be upregulated. Since glutamine uptake also promotes lipids biosynthesis via reductive carboxylation, thus both glutamine uptake and lipids biosynthesis might be potential therapeutic targets. Inhibition of fatty acid synthase has been shown to have a potent effect in vitro in ccRCC cell lines; however, more work will be needed before this is translated into clinical trials. Preclinical studies have shown that cancer cells shift their metabolism to glutamine metabolism to support anabolism and growth.[27] In *VHL*-deficient tumor cells, HIF2-alpha expression is sufficient to induce reductive carboxylation because of reduced intracellular citrate levels.[28-31]

FIGURE 1. Clear Cell Renal Cell Carcinoma

High-grade, high-stage ccRCC present a metabolic shift toward aerobic glycolysis, decreased oxidative phosphorylation, and increased glutamine metabolism. This metabolic adaptation is supported in part by activation of the PI3K/Akt, mTOR, and HIF pathways.

Glutamine starvation and glutaminase inhibitors were both lethal to *VHL*-deficient tumor cells in vitro and in preclinical animal models suggesting that glutamine metabolism may be a therapeutic target for *VHL*-deficient ccRCC, alone or combined with other approaches. The development of glutaminase inhibitors for ccRCC therapy is currently being evaluated in early phase clinical trials.

OXIDATIVE STRESS RESPONSE IN CLEAR CELL RENAL CELL CARCINOMA

The high-energetic needs of tumor cells, aerobic glycolysis, inhibition of autophagy, and rapid cell proliferation, all lead to an increased oxidative stress.[32,33] Oxidative stress caused by unbalanced accumulation of reactive oxygen species (ROS), has been shown to promote tumor growth by inducing DNA damage and gene mutations or by activating signaling pathways promoting cell proliferation.[32] However, how to therapeutically target or manage tumors' oxidative stress response is still under study and it is unclear whether ROS scavengers or inducers might be beneficial. In ccRCC, both approaches have been evaluated in preclinical models. Agents affecting glutathione metabolism (glutaminase inhibitors), for example, or inducing endoplasmic reticulum stress (proteasome inhibitors and Hsp90 inhibitors) have been shown to be effective in preclinical models.[30,34]

TYPE II PAPILLARY RENAL CELL CARCINOMA

Type II papillary RCC can occur in both a sporadic (nonhereditary) and inherited form. Hereditary leiomyomatosis

and renal cell carcinoma (HLRCC) is a hereditary cancer syndrome in which affected individuals are at risk for the development of cutaneous and uterine leiomyomas and an aggressive form of type II papillary RCC.[35] The most prevalent gene mutation(s) responsible for sporadic papillary type II tumors are still unknown; however, studies have reported mutations of genes in the Nrf2 complex (Nrf2, KEAP1, CUL3).[36]

UNDERSTANDING THE METABOLIC ADAPTATION OF HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CARCINOMATUMORS

In 2002 Tomlinson et al determined that *FH*, a gene encoding the TCA enzyme fumarate hydratase, was responsible for HLRCC.[37] It is estimated that approximately 15% to 20% of patients bearing a *FH* germ-line mutation will develop kidney tumors. Loss of FH enzyme function leads to impaired oxidative phosphorylation, a metabolic shift to aerobic glycolysis, and accumulation of the metabolite fumarate.[38-40] In patients with HLRCC-associated kidney tumors, HIF1-alpha and GLUT1 are overexpressed and tumors are highly [18F]fluorodeoxyglucose-avid on PET imaging.[39,40] FH-deficient tumor cells are notably dependent on glucose for ATP production as well as on glutamine for citrate, glutathione, and lipid biosynthesis. Increased amounts of the metabolite fumarate accumulate because FH-deficiency drives multiple biologic processes including inhibition of prolyl hydroxylase and stabilization of HIF1-alpha, supporting both

aerobic glycolysis (GLUT1/4, LDHA) as well as angiogenesis (e.g., vascular endothelial growth factor).[39] Aerobic glycolysis in HLRCC-associated FH-deficient papillary RCC cells produces increased ATP, leading to downregulation of the energy-sensing master regulator, AMPK.[22] Therapeutic strategies targeting aerobic glycolysis with silencing of LDHA or activators of AMPK have shown promising preclinical effects.[22,41]

OXIDATIVE STRESS RESPONSE IN HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CARCINOMA

FH-deficient tumor cells are characterized by oxidative stress due to elevated aerobic glycolysis and fumarate accumulation.[42,43] Targeting this redox imbalance by further increasing ROS has shown promise in preclinical studies.[44] In addition to its role on inducing ROS, fumarate accumulation is also critical in supporting the antioxidant response via the inhibitory succination of the Kelch-like ECH-associated protein 1 (KEAP1).[45,46] KEAP1 is the endogenous Nrf2 inhibitor and promotes targeting Nrf2 for proteosomal degradation. Nrf2 is a transcription factor critical for the antioxidant response by transcriptionally activating genes with antioxidant response element sequences, including NQO1 and HMOX.[47] The antioxidant signature of Nrf2 pathway activation has been found in both sporadic papillary type II tumors as well as HLRCC-associated kidney tumors, providing a potential therapeutic approach targeting this pathway.[46]

In studies conducted to develop a therapeutic approach targeting the Nrf2 pathway in FH-deficient type II papillary RCC, we recently showed that the activity of tyrosine kinase ABL1 was critical for Nrf2 nuclear translocation opening a new perspective on how to target this pathway[21] (Fig. 2). Based on current understanding of the mechanisms supporting HLRCC tumor cell survival with aerobic glycolysis needed to provide ATP and NRF2 antioxidant response pathway needed to cope with this extreme metabolism, it is reasonable to speculate that targeting both pathways simultaneously might have a promising effect. A phase II trial for patients with advanced papillary type II tumors (NCT01130519) using bevacizumab to inhibit angiogenesis and erlotinib to inhibit EGFR and modulate glucose and lipid metabolism via regulation of the PI3K/Akt pathway is currently underway.[48] In addition, we have also developed a therapeutic strategy targeting glycolysis and Nrf2 transcriptional activity via ABL1 inhibition.[21] We showed that ABL1 supports glycolysis in an mTOR-dependent manner and promotes Nrf2 transcriptional activity by indirectly allowing its nuclear translocation. Promising results were found in in vivo experiments in HLRCC xenograft models using vandetanib (a potent ABL1 inhibitor) as a single agent and when combined with the AMPK-activator metformin. A clinical trial evaluating the effect of vandetanib and metformin in patients with sporadic as well as HLRCC-associated type II papillary RCC is under development.

CONCLUSION

Over the past two decades significant progress has been made in our understanding of the molecular mechanisms of RCC.

FIGURE 2. Hereditary Leiomyomatosis and Renal Cell Carcinoma
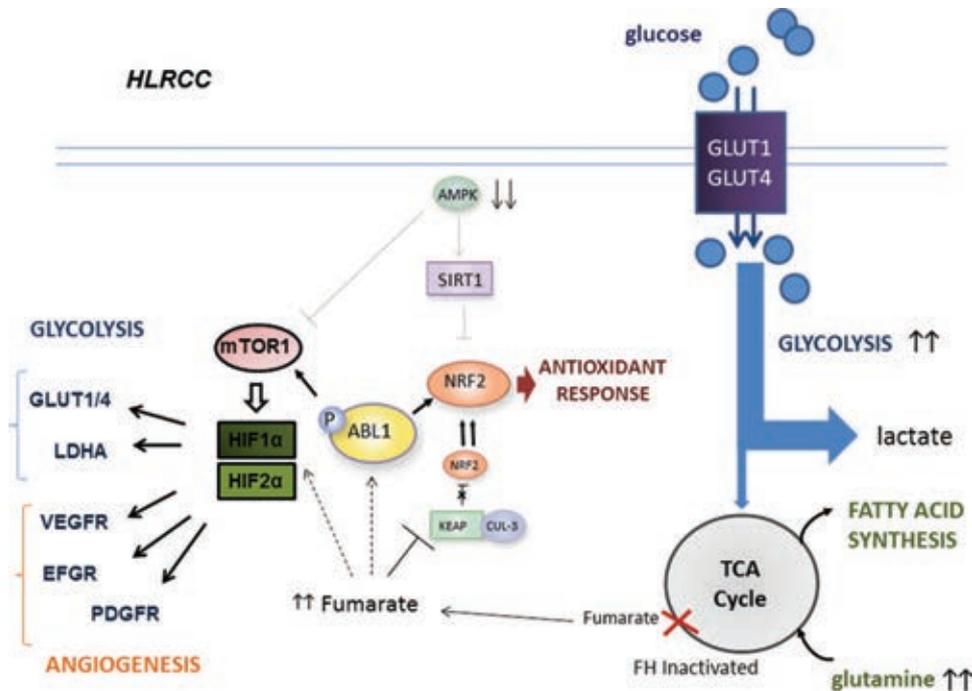
FH-deficient tumor cells are characterized by elevated aerobic glycolysis and oxidative stress. Accumulation of the oncometabolite fumarate promotes Nrf2 antioxidant response transcriptional activity via KEAP1 inhibition and ABL1 activation. ABL1 also regulates aerobic glycolysis by activating the mTOR/HIF pathway.

Ten years ago we had very limited options for the treatment of patients with advanced RCC. We currently have seven approved agents for patients with advanced RCC and have some potential approaches that could represent a new era of targeted therapies and precision medicine designed to target metabolic and stress response pathways critical to tumor survival. The development of new bioinformatic tools will certainly further improve our understanding of the metabolic basis of kidney cancer and will hopefully provide the basis for the development of effective forms of therapy for patients with this disease.

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Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

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