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BREAST CANCER
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Shelly Gunn, MD, PhD

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Pathologic complete response (pCR) is the absence of residual cancer following neoadjuvant chemotherapy. Rossi and colleagues describe pCR of a woman with HER2-positive breast cancer following a single cycle of treatment. Their findings suggest that research focusing on fewer than the current standard number of cycles of neoadjuvant therapy may help define the optimal treatment to obtain pCR in HER2-positive breast cancer.

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Immunotherapy for Triple-Negative Breast Cancer: A Focus on Immune Checkpoint Inhibitors

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Dr Martin offers his insights on current and emerging treatment approaches in patients with marginal zone lymphoma (MZL), with a focus on mild forms of the disease and patients with refractory or relapsed MZL.

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Chairman's Letter

Michael J. Hennessy, Sr

This month's issue of the *American Journal of Hematology/Oncology®* addresses various topics involving breast cancer, including human epidermal growth factor receptor 2 (HER2) assays, pathologic complete response (pCR), and the potential role of immunotherapy in triple-negative breast cancer (TNBC). Rounding out the issue is a manuscript that addresses radiotherapy in gastric cancer.

In a commentary by Shelly Gunn, MD, PhD, of Targeted Genomics and Precision Pathology Services, the topic of HER2 testing that results in an "equivocal" assessment is discussed. Her manuscript, "Redefining HER2-Equivocal Breast Cancers: Lessons Learned From Genomic Pathology," raises the following questions: are immunohistochemistry and dual-probe in situ hybridization tests giving the wrong answer 20% of the time or, could these tests be giving the correct answers and we are misinterpreting the data? Dr Gunn suggests that a strategy for reporting unequivocal biologically accurate results using existing FDA-approved testing methods is preferable to developing new HER2 assays.

Isolina R. Rossi, BS, a student at Rush Medical College, Chicago, and colleagues describe a case report in which a patient experienced a pCR following systemic neoadjuvant therapy. The investigators note a high rate of pCR in HER2-positive, hormone receptor-negative patients with breast cancer who are treated with neoadjuvant docetaxel (T), carboplatin (C), trastuzumab (H), and pertuzumab (P) (TCH+P). Because of adverse events, the TCH+P treatment was aborted, but resulted in a pCR of grade 2 invasive ductal carcinoma.

Drs Dua and Tan explore the role of immunotherapy in TNBC. They note a lack of actionable targets, minimal targeted therapies, and a relatively poor prognosis associated with this clinical setting. In "Immunotherapy for Triple-Negative Breast Cancer: A Focus on Immune Checkpoint Inhibitors," the investigators focus on the emerging data of immune checkpoint inhibitors in the treatment of TNBC.

Although there has been great progress in the management of gastric cancer, Repka and colleagues write that there is clear opportunity for improvement. Their manuscript, "The Role of Radiotherapy in the Management of Gastric Cancer," provides a comprehensive discussion about advances in radiotherapy techniques and their applicability to gastric cancer.

The CME article this month focuses on current treatment options for patients with marginal zone lymphoma (MZL). Peter Martin, MD, MS, an associate professor of medicine in the Division of Hematology/Oncology at Weill Cornell Medicine discusses the unmet needs of patients, particularly those with localized intestinal MZL who may not be symptomatic, but who are at risk of having worsening symptoms. In this setting, providing occasional therapy to prevent symptoms might be an option over rituximab plus chemotherapy. For patients who are refractory or relapsed, there is a need for identifying therapies that work in ways different than chemotherapy.

Thank you for reading.

Michael J. Hennessy, Sr
Chairman and Chief Executive Officer

From the Editor

This issue of the *American Journal of Hematology/Oncology®* contains an important editorial and call to action for a change in how we interpret *HER2* at the genomic level. As one of the early discovered gene amplifications that soon became a "druggable" target, HER2 analysis had a shaky start. One of the initial antibodies used to qualify patients for the trastuzumab trials was a rabbit polyclonal antibody that was rather sensitive, but not very specific. As monoclonal antibodies were validated to perform this task, there was still concern about tissue processing and accuracy—either false positives due to "antigen retrieval" using microwave heating or false negatives due to formalin fixation over a long weekend and loss of the epitope. The advent of fluorescence in situ hybridization (FISH) promised to solve this problem, in particular for *HER2*, where overexpression was felt to be uniformly driven by excess gene copy number and appeared to better predict clinical response to single-agent trastuzumab therapy.[1]

Debu Tripathy, MD
Editor-in-Chief

Fast forward to the last 5 years and several iterations of American Society of Clinical Oncology/College of American Pathologists guidelines that have tried to accommodate both single- and dual-probe (normalized) FISH to define positivity and equivocal results—which have become the bane of clinical decision making and heated discussions at tumor boards. This is in distinction to next-generation sequencing assays that make amplifications calls on the basis of copy number alone since whole chromosome polysomy is less common than loss or gain at loci at or around the centromere to which dual-probe FISH results are normalized and there is evidence that cases with low HER2 expression and borderline *HER2* copy number may not benefit from trastuzumab.[2] As Dr Gunn points out, we may be better off simply casting off centromeric normalization and use absolute *HER2* copy number. Of course, this may lower the number of equivocal results, but it will be very difficult to prove that this allows for more accurate decision making and treatment assignment and, ultimately, improved outcomes. Data from NSABB B-47 testing adjuvant trastuzumab in HER2-low cases and correlations with newer genomic assays may eventually provide more definitive data to change the standard.[3]

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Commentary—Redefining HER2-Equivocal Breast Cancers: Lessons Learned from Genomic Pathology

Shelly Gunn, MD, PhD

Abstract

In the era of precision medicine, human epidermal growth factor receptor 2 (*HER2)* is the most important predictive and prognostic biomarker in breast cancer. The HER2 status of a patient's tumor can be analyzed at the protein level by immunohistochemistry (IHC) and at the chromosome level by in situ hybridization (ISH) techniques to determine the average *HER2* gene copy number. Yet, despite these 2 complementary methods for HER2 testing, there remains a subset of high-risk breast cancer patients (>20%) whose HER2 status is reported as "equivocal," an assessment that provides no useful information about how to treat the patient. Given there are 2 FDA approved HER2 assays readily available in the clinical laboratory, the currently confused state of HER2 testing in breast cancer is perplexing and raises the following questions: are IHC and dual-probe ISH giving the wrong answer 20% of the time, or alternatively, could these tests be giving the correct answers and we are misinterpreting the data? For the past decade, genomic pathologists have used chromosomal microarrays (CMAs) as a DNA-based approach for obtaining high-resolution images of *HER2* gene status on chromosome 17. These studies provide confirmation that ISH is a reliable method for determining average *HER2* gene copy number, and it is the HER2 ratio denominators (cep17 or alternative probes) that can introduce instability into the final results. However, even though CMA provides more detailed information about chromosome 17 status in breast cancer than conventional cytogenetics or FISH, the complexity of the method and interpretation make it impractical for routine use by the clinical laboratory as a HER2 testing method. Thus, IHC and fluorescence in situ hybridization will remain for the foreseeable future, the mainstay of HER2 testing in breast cancer. The current challenge is thus not to introduce a new HER2 assay into the clinical laboratory but rather to develop a strategy for reporting unequivocal, biologically accurate results using existing FDA-approved testing methods.

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Introduction

It has been 3 decades since the human epidermal growth factor receptor 2 (*HER2*) was identified as an oncogenic driver of human breast carcinomas.[1] Now, as medical oncology enters the era of precision medicine, *HER2* is still the most important predictive and prognostic biomarker in breast cancer.[2] The HER2 status of a patient's tumor can be analyzed at the protein level by immunohistochemistry (IHC) to visualize cell-surface receptor targets for anti-HER2 directed therapy. Additionally, HER2 status can be evaluated at the chromosome level by in situ hybridization (ISH) techniques to determine the *HER2* gene copy number within the cell nucleus. Yet despite these 2 FDA-approved methods for HER2 testing and the many biotechnological advances in clinical pathology laboratory medicine, there remains a subset of high-risk patients with breast cancer (>20%) whose HER2 status is reported (often after multiple rounds of testing) as "equivocal."

Classifying a patient's tumor as HER2 equivocal gives clinicians no insight into the tumor's HER2 biology, nor does the word provide any useful information about how to treat the patient. In the Merriam-Webster dictionary, the adjective "equivocal" is defined as "subject to 2 or more interpretations and is usually used to mislead or confuse." Certainly clinicians and patients who have received breast cancer prognostic marker reports with HER2 equivocal results would agree that this term is both misleading and confusing. In my pathology consultation practice, many such cases have been referred to me, including this recent example:

Case History

A 69-year-old woman presents with a grade 2, <2 cm, node negative, strongly estrogen receptor–positive (ER+)/progesterone receptor–positive (PR+) tumor with HER2 initially reported as negative based on IHC score of 1+. The case was reflexed to FISH [fluorescence ISH] due to "histopathologic discordance" and reported as equivocal. The HER2/D17Z1 (chromosome 17 centromere) FISH ratio was 1.4 (negative) "to be interpreted with caution" due to the average copy number signals per cell of *HER2* 4.6 and D17Z1 3.2 (equivocal). The case was further reflexed for chromosome 17 "alternative probe" FISH where the results were reported as positive based on the HER2/TP53 ratio of 2.3 and HER2/SMSCR ratio of 2.0 [TP53 and SMSCR are chromosome 17 regions].

Is it any wonder that oncologists often feel misled and confused by pathology reports for HER2 status in breast cancer? The above case is just 1 example of why incalculable numbers of hours and healthcare dollars are continually spent on HER2 testing methods to "resolve" equivocal *HER2* breast cancer into clearly actionable HER2-positive or HER2-negative categories. The collective effort to create a binary, 2-tier framework around HER2 status in breast cancer is understandable given that oncology clinical practice guidelines have clearly actionable treatment directives only for unequivocally positive or negative HER2 results. High-risk tumors with a combination of low HER2 protein expression and nonamplified *HER2* gene copy number fit neither of these categories. Yet tumors with low HER2 protein expression represent a significant subset of breast cancer cases. Could these tumors be trying to announce their biological reality by consistently showing 1 to 2+ protein and <6 copy numbers after repeated rounds of testing?

Since the term "equivocal *HER2*" was introduced as part of the first College of American Pathologists/American Society of Clinical Oncology (CAP/ASCO) guidelines published in 2007, the term has become synonymous with a third category of breast cancer.[3] Following implementation of updated CAP/ASCO guidelines in 2013, the number of breast cancer cases falling into the equivocal category has increased, along with the number of additional tests that must be performed to resolve equivocal results.[4, 5] Within this equivocal category, clinicians often end up with a collection of results from repeated and alternative testing methods used to attempt to resolve the equivocal HER2 status of the tumor. These test results often disagree as to whether the tumor is HER2-positive, HER2-negative, or something in between. The discordant test results may arise from IHC, ISH, alternative chromosome 17 probes, RNA multigene expression arrays, 21-gene recurrence score assays, DNA microarrays, and serum HER2 protein analysis, but only 2 of the aforementioned tests—IHC and FISH—are actually FDA approved for reporting HER2 status in breast cancer!

Given then that there are 2 excellent HER2 assays (IHC and ISH) readily available in the clinical laboratory, the currently confused state of HER2 testing in breast cancer is perplexing and raises some questions:

- Are IHC and 2-probe ISH giving wrong answers 20% of the time, consistently, requiring alternative testing methods to resolve discrepancies?
- Alternatively, could IHC and ISH be giving correct answers, but we misinterpret the data and thus miss the true HER2 biology of HER2 "equivocal" tumors?

Seeking answers to these questions, multiple genomic pathology groups have analyzed breast cancers that have been characterized by IHC and FISH using comparative genomic hybridization, also called chromosomal microarrays (CMAs).[6-10] CMAs provide a DNA-based approach to chromosome analysis with the capability of producing a high-resolution view of the *HER2* gene on chromosome 17. The chromosome "ratio plot" allows simulated visualization of the p arm, q arm, pericentromeric region, and *HER2* gene within the 17q12 amplicon. These high-resolution CMA images of *HER2* gene status on chromosome 17 in multiple types of breast cancer have revealed the following interesting findings:

- CMA studies provide confirmation that ISH is a reliable method for determining *HER2* gene copy number independent of a ratio as long as formalin-fixed paraffin-embedded tissue handling is within CAP/ASCO guidelines for formalin fixation times.
- CMAs have revealed that tumors with gains of entire copies of chromosome 17 (polysomy 17) occur in <10% of breast cancers even though the HER2/cep 17 ratio used in dual-probe FISH is intended to correct for this biological phenomenon (cep 17 is another area of chromosome 17 used as a denominator in ratios). Instead of polysomy, many tumors contain segmental gains on chromosome 17, particularly on the long arm.[11,12] A standard definition of HER2 "amplification" by genomic copy number analysis (including CMA) has not yet been established.
- CMA allows visualization of relative gains or losses of chromosome 17 regions used as the ratio denominator (cep17, *TP53*, SMSCR, *RARA*), causing the ratio to skew towards false negative or false positive.
- Although CMA provides more detailed information about chromosome 17 status in breast cancer than do conventional cytogenetics or FISH, the complexity of the method and interpretation make it impractical for routine use by the clinical laboratory. Thus IHC and FISH will remain, for the foreseeable future, the mainstay of testing for HER2 status in breast cancer.

The above observations from genomic pathology help explain many of the primary problems with current HER2 testing, and they suggest strategies that could potentially improve results reporting.

1. Is it time to move away from dual-probe testing and the HER2/cep17 ratio to a single-probe approach? Beginning with the first Southern blots used to identify *HER2* gene amplification in breast carcinomas, *HER2* gene testing has historically been reported as a ratio. In the initial studies, *HER2* gene DNA was compared with DNA of other genes such as *ARG1* as a nonamplified internal control.[1] In the era of FISH, a ratio of HER2 gene copy number per nucleus to chromosome 17 centromere copy number per nucleus is used as an internal control to "correct for" polysomy 17. However, from CMA studies we know that single-probe ISH is giving the correct answer, and it is the ratio

that can introduce instability by skewing the result toward a false positive or a false negative. This ratio skewing is a result of the segmental gains or losses within chromosome 17 that are more common than polysomy 17 in breast cancer.[7] In addition, the process of interchanging alternative denominator probes does not alter the gene copy number of the numerator. According to current CAP/ASCO guidelines, a tumor with 4 to 6 copies of the *HER2* gene will be called "HER2 equivocal" provided the denominator generates a ratio less than 2.0. Although reporting average *HER2* gene copy number would thus seem to be the most straightforward approach, substantial supporting data do not yet exist for making such a change. Therefore, pathologists will need to continue to critically evaluate FISH results based on the numerator, denominator, IHC findings, and the patient's clinical presentation.

2. How can we create an unequivocal reporting system? The current strategy of trying to fit all breast cancers into 2 HER2 categories for protein expression and *HER2* gene copy number may not be representative of the true biological spectrum of HER2 results. A 3-tier system including a borderline amplified group was described by Ross and colleagues in 1998 using data from multivariate analysis of a subset (n = 220) of node-negative breast cancers derived from 324 cases reported by Press and colleagues in 1997.[13-15]

A more recent retrospective study by Press et al re-interpreted enrollment and outcomes data from the Breast Cancer Research Group clinical trials using 2013 CAP/ASCO guidelines for FISH. Findings from more than 10,000 patients enrolled in the clinical trials support the original FDA-approved criteria (in which there is no equivocal category) to be strongly predictive of treatment response.[16] In this authors' opinion, and based on these previous studies, a 3-tier system for HER2 reporting, one that recognized 3 categories of HER2 biology, could be considered an unequivocal reporting strategy: tumors showing high-level gene amplification with high (3+) protein expression would be HER2-positive, tumors with borderline gene amplification (<6 copies) and low-level protein expression would be HER2-low; and tumors with no gene amplification and no protein expression would be HER2-negative. Response to Herceptin in the HER2-low category of tumors is currently being studied in the National Surgical Adjuvant Breast and Bowel Project (NSABP)-B47 trial. This randomized phase III trial is comparing chemotherapy alone with chemotherapy plus trastuzumab in more than 3000 women with node-positive or high-risk node-negative HER2-low invasive breast cancer.[17]

The specific aim is to determine whether the addition of trastuzumab improves invasive disease–free survival in women with high-risk breast cancer reported as HER2-low by IHC and FISH. Eligibility for the trial is determined by an IHC score of 1 to 2+ and by a HER2-to-chromosome enumeration probe ratio of <2.0, which, together, document the presence of HER2 target receptors on the tumor cell surface and lack of *HER2* gene amplification in the cell nucleus.

3. Are there currently any treatment recommendations for the HER2-low category of breast cancer? The NSABP-B47 trial began in January 2011, and its estimated primary completion date is in 2017. Although there are no current treatment recommendations for HER2-low tumors, identifying this subtype in high-risk patients will give clinicians insight into the HER2 biology of their patients' tumors and provide unequivocal categorization of the HER2 status.

In summary, it may be time to replace ratio reporting with single-probe ISH, and to categorize breast tumors with average *HER2* gene copy number <6 and 1-2+ protein expression as HER2-low. Recognizing this distinct genomic subtype on pathology reports will give a clinician critical information about a patient's HER2 biology, while saving time and healthcare dollars that are currently being spent trying to transform HER2-low tumors into those that can be definitively called HER2-positive or HER2-negative. We must await the results of the NSABP-B47 trial for guidance as to how to best treat this subset of high-risk patients, but to recognize this genomic subtype now would at least identify the HER2-low tumors and "give them their seat at the table," as one of my pathology colleagues has eloquently stated.

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Disclosures: Dr Gunn discloses that she has been a speaker for Roche/Genentech.

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The Role of Radiotherapy in the Management of Gastric Cancer

Michael C. Repka, MD; Mohamed E. Salem, MD; and Keith R. Unger, MD

Abstract

Over the past half-century, the incidence of gastric cancer in the United States has steadily declined. Furthermore, with improvements in detection, staging, and treatment, the overall mortality rate from gastric cancer has similarly decreased. In spite of these gains, the overall prognosis for patients with gastric cancer remains poor, with approximately 30% surviving 5 years past their initial diagnosis. The optimal therapeutic strategy for patients with gastric cancer, particularly those classified as locally advanced, remains undefined. Although surgical resection is the mainstay of treatment for nonmetastatic gastric cancers, significant controversy persists over the role of extended lymphadenectomy. Selecting an ideal treatment strategy in the neoadjuvant or adjuvant setting is perhaps even more challenging, as randomized data have demonstrated benefits to multiple approaches, each with its own unique set of strengths and weaknesses. Further complicating matters is a recent epidemiologic shift, reflected in a higher proportion of tumors located at the gastric cardia and a higher relative incidence of the diffuse histologic subtype. Additionally, some existing evidence is extrapolated from published results of patients with adenocarcinoma of the esophagus, and many key studies included patients with cancers of the gastroesophageal junction.

In this article, we review the evidence for the different treatment paradigms with a particular focus on the role of radiotherapy. We additionally evaluate the role of radiotherapy for patients with unresectable or metastatic disease. Finally, we discuss future directions in gastric cancer management, as well as the evolution of radiotherapy technique over the past 2 decades, which have witnessed profound improvements in the ability to conformally deliver dose. Radiotherapy continues to play a crucial role for many patients with gastric cancer in both the curative and palliative settings. Future research will help clarify its use in the burgeoning era of immunotherapy and targeted systemic agents.

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Introduction

According to recent estimates, approximately 28,000 new cases of gastric cancer will be diagnosed in the United States in 2017.[1] There has been a significant downward trend in the overall incidence of gastric cancer in recent years. The incidence per 100,000 people decreased from 12 in 1976 to 6.7 in 2013, and it is still declining.[2] Gastric cancer mortality rates have also similarly decreased—the 5-year relative survival for all patients has doubled since the mid-1970s. Unfortunately, despite these gains, about 70% of patients diagnosed with this disease will not be alive 5 years post diagnosis. Even for the subgroup of patients who present with localized disease without regional lymph node metastasis, the 5-year relative survival rate is an unsatisfactory 64%. Although great progress has been made in the management of gastric cancer, there is clear opportunity for continued improvement.

Worldwide, gastric cancer remains among the most commonly diagnosed malignancies, although the international annual incidence is also falling.[3] The causes of gastric cancer remain multifactorial but perhaps the 2 strongest predisposing factors are infection with *Helicobacter pylori* and frequent ingestion of salted or smoked foods.[4] While in Western nations the initial decrease in gastric cancer incidence began in the early to mid-20th century, a comparable trend has been noted only more recently in endemic areas such as Japan or South Korea.[3] The widespread availability of food refrigeration and the successful treatment of active *H. pylori* infection have been identified as key interventions leading to the lower prevalence of gastric cancers. Nonetheless, although the worldwide per-capita rates of gastric cancer are decreasing, the overall number of new cases continues to grow with the increasing worldwide population and the median age at diagnosis continues to decrease.

In accordance with changes in domestic and worldwide incidence, shifts in histologic and distribution patterns have also occurred over the past several decades. The most common intestinal histologic subtype carries a better prognosis,[5] but the diffuse histologic subtype, which carries a poor prognosis, typically affects younger patients and does not appear as dependent on environmental factors as does the intestinal histologic subtype. The diffuse histologic subtype now represents approximately 20% of gastric cancer diagnoses in recently reported American studies.[6,7] Furthermore, a notable anatomic shift has occurred: Tumors of the gastric cardia have become more

prevalent while the incidence of distal tumors has decreased.[8] This trend parallels that seen in esophageal cancer, which may be a significant confluence due to the similar origin and behavior of gastric cardia tumors when compared with adenocarcinomas of the gastroesophageal junction.[9]

Historical Management of Gastric Cancer and the Role of Radiotherapy

The sole proven curative intervention for gastric cancer is radical surgery, although there may be a role for endoscopic mucosal resection in patients with tumors limited to the lamina propria or muscularis mucosae without evidence of lymph node involvement.[10] Radical resection of a gastric tumor that is limited to the submucosa can be curative; however, in patients with deeper tissue invasion or lymph node metastases, this procedure alone yields poor patient survival outcomes. Early randomized trials examined surgical techniques used in the management of gastric cancer in order to clarify the role of partial versus total gastrectomy. Multiple European studies demonstrated similar outcomes between partial and total gastrectomy for patients with distal tumors; however, total gastrectomy remains the standard of care for proximally located tumors.[11,12]

The role of extended lymphadenectomy in the treatment of gastric cancer remains controversial, despite a preponderance of data from large, randomized trials. Surgical lymph node levels are usually classified by the Japanese Gastric Cancer Association system and are used to determine the extent of lymphadenectomy needed. Briefly, removal of stations 1 to 6 (perigastric lymph nodes) is considered a D1 dissection, whereas removal of stations 7-11 (celiac, common hepatic, and splenic lymph nodes) is considered a D2 dissection. More extensive lymphadenectomy, including removal of the para-aortic nodes, has been evaluated in the randomized setting, but it does not appear to confer a benefit over D2 dissection.[13] Furthermore, the role of D2 resection, while accepted as standard in Japan, remains controversial in Europe and the United States. Although D1 dissection is associated with less operative morbidity and mortality than a D2 procedure, 15-year follow-up of patients in a Dutch randomized trial revealed a significant locoregional recurrence (LRR) benefit to carrying out the more extensive D2 surgery.[14,15] Nonetheless, the high frequency of local failure and underwhelming patient survival rates observed in these trials suggest that surgery alone is unacceptable for all patients except those with early-stage disease.

An early trial from the British Stomach Cancer Group—which randomized patients to observation, adjuvant radiotherapy, or adjuvant chemotherapy following surgical resection—failed to demonstrate an overall survival (OS) benefit. Outcomes were generally discouraging; patient 5-year OS was only about 17% in any treatment group.[16] However, there was a large reduction in LRR with the addition of adjuvant therapy to surgery. Radiotherapy in particular decreased the LRR from 27% to just 10%, suggesting that a more comprehensive treatment approach might yield better outcomes. An additional randomized trial carried out in China evaluated the role of neoadjuvant radiotherapy prior to radical resection for adenocarcinoma of the gastric cardia.[17] In this study, patients either underwent surgery alone or received a preoperative dose of 40 gray (Gy) to the gastric cardia, gastroesophageal junction, and limited regional lymph nodes. A significant OS advantage (absolute risk reduction of approximately 10% at 5 years) was noted in the group receiving the neoadjuvant radiotherapy. The role of neoadjuvant radiation therapy, a strategy successfully applied to the management of other gastrointestinal cancers, is being further evaluated in ongoing clinical trials.

The Role of Radiotherapy in the Adjuvant Setting

The benefits of adjuvant radiotherapy in the management of gastric cancer became more clearly defined in 2001 after the publication of the landmark Intergroup 0116 trial.[18,19] Eligible patients had at least stage Ib adenocarcinoma of the stomach or gastroesophageal junction using the 3rd edition American Joint Committee on Cancer (AJCC) staging manual, although the majority of tumors were located in the distal stomach, were stage T3 or T4, and had associated nodal disease at diagnosis. Patients were randomized to undergo observation or adjuvant chemoradiotherapy following surgical resection. Chemotherapy consisted of 5 cycles of bolus 5-fluorouracil (5-FU) with leucovorin, and radiation therapy entailed delivery of a 45 Gy dose to the tumor bed and regional lymph nodes, primarily using opposed anterior and posterior fields concurrently with the second and third cycles of chemotherapy.

OS following adjuvant chemoradiotherapy was markedly improved: a median OS of 36 months was achieved in patients receiving adjuvant therapy compared with 27 months in those who underwent surgery alone. Additionally, the local failure rate (2% vs 8%) and regional failure rate (22% vs 39%) were better following adjuvant chemoradiotherapy. Distant metastatic disease rates were similar between the 2 arms: 16% following chemoradiotherapy plus surgery and 18% following surgery alone. These data confirm the benefit of adjuvant chemoradiotherapy in the postoperative setting, particularly in node-positive patients who receive no neoadjuvant therapy.

Despite these positive findings, several criticisms have been leveled against this trial. As expected, toxicity rates were significantly higher in patients undergoing chemoradiotherapy. Thirty-three percent of patients in the chemoradiotherapy arm suffered from grade 4 acute toxicity, and 4 treatment-related deaths were observed (secondary to cardiac toxicity, neutropenic sepsis, pulmonary fibrosis, and central line–associated fungemia). Although certainly concerning, these effects can likely be minimized by using modern chemotherapy delivery and radiotherapy techniques. Extrapolating from experience in rectal adenocarcinoma and nonrandomized gastric cancer studies, the use of either continuously infused 5-FU or oral capecitabine in lieu of bolus 5-FU is associated with less toxicity and likely achieves equivalent outcomes.[20,21] Moreover, the delivery of radiotherapy has undergone several technological revolutions since this trial was carried out. Perhaps most significantly, highly conformal radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT),

have been introduced. A comprehensive discussion of advances in radiotherapy techniques and their applicability to gastric cancer is addressed later in this review.

The limited extent of lymph node dissection performed in most patients enrolled in the Intergroup 0116 trial has been a source of considerable criticism. Although a full D2 lymph node dissection was recommended by the investigators, only 10% of enrolled patients underwent this procedure. Furthermore, only 36% of patients underwent a D1 resection, while the remaining 54% of patients were treated with a D0 resection. Given the high rate of lymph node involvement, many have argued that chemoradiotherapy may have compensated for suboptimal lymph node dissection and may be unnecessary in patients who undergo more extensive surgery.

To address this shortcoming, the Korean randomized phase III ARTIST trial evaluated adjuvant chemoradiotherapy in patients with pathologic AJCC seventh edition stage IB-IIIC who had undergone R0 resection with full D2 lymphadenectomy.[22] Previous studies carried out in Japan and Korea, the Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) and Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) trials, respectively, demonstrated an OS benefit following the addition of adjuvant chemotherapy to more thorough surgical resection. In the investigational arm of the ARTIST trial, patients received 2 cycles of capecitabine and cisplatin together (XP) prior to chemoradiotherapy with capecitabine, followed by another 2 cycles of XP. The XP-only group was chosen as the control arm. The median follow-up was 5 years, after which time there were no significant differences in disease-free survival (DFS) or OS. There was a trend toward improved DFS following the use of chemoradiotherapy (hazard ratio, 0.74; $P = .09$), which was the primary endpoint of the trial. Posthoc analyses revealed statistically significant DFS benefits for those patients with either node-positive disease or intestinal-type histology. A follow-up trial, the ARTIST 2, is currently accruing a similar patient cohort with positive lymph nodes, which is randomizing patients to either S-1 (an oral combination of tegafur, gimeracil, and oteracil), S-1 with oxaliplatin, or chemoradiotherapy. No results from this trial are currently available.[23]

The results discussed in this section suggest that postsurgical adjuvant chemoradiotherapy should be routinely used in patients who have undergone curative surgical resection in the absence of neoadjuvant therapy with additional risk factors such as pathologic invasion of the muscularis propria or positive lymph nodes, particularly in the setting of D1 or D0 lymphadenectomy.

Role of Chemoradiotherapy in the Era of Perioperative Chemotherapy

While the Intergroup 0116 trial established adjuvant chemoradiotherapy as the standard of care for resected gastric cancer in the United States, a few alternative treatment strategies have been employed. Foremost among these paradigms is perioperative chemotherapy, which was established following publication of the Medical Research Council's MAGIC trial in 2006.[24] Notably, this trial included tumors of the stomach, gastroesophageal junction, and esophagus, although the majority of tumors (74%) were located in the stomach. Patients who were randomized to perioperative chemotherapy were scheduled to receive 3 cycles of combination epirubicin, cisplatin, and 5-FU (ECF) prior to radical resection as well as 3 cycles of ECF in the postoperative adjuvant setting. Perioperative chemotherapy resulted in more primary tumor downstaging, and it increased both OS and progression-free survival. Additionally, patients who actually received neoadjuvant chemotherapy and underwent radical surgery were more likely to undergo R0 resection, although this finding did not achieve statistical significance on intention-to-treat analysis. However, treatment completion was challenging for most patients, as only 42% of those enrolled were able to complete the full chemotherapy schedule. Furthermore, no patient had a pathologic complete response (pCR) at the time of surgical resection, following 3 initial cycles of ECF.

Several other trials have examined the role of perioperative chemotherapy with similar results, such as the French FNLCC/FFCD and EORTC 40954 trials.[25,26] Although an OS benefit was not observed in the EORTC 40954 trial, which was closed early, secondary to poor accrual, both trials demonstrated improved R0 resection rates with neoadjuvant chemotherapy.

A meta-analysis comprising many of these trials confirmed the positive effect of neoadjuvant chemotherapy on OS, R0 resection rate, and primary tumor downstaging.[27] As a result, there has been fierce debate over the past decade regarding whether adjuvant chemoradiotherapy or perioperative chemotherapy provides the best outcomes in patients with locally advanced gastric cancer.[28] Although the ARTIST trial shed some light on this question, extrapolating these results is problematic for numerous reasons. Fortunately, the recently presented CRITICS trial, which is not yet available in manuscript form, should help guide treatment decisions.[29] In this study, all patients received 3 cycles of neoadjuvant ECF or epirubicin, oxaliplatin, and 5-FU (EOF) prior to undergoing definitive surgical resection. Following surgery, patients were treated according to preoperative randomization, which consisted of an additional 3 cycles of ECF or EOF or chemoradiotherapy with concurrent XP. Extent of surgical resection was greater than that seen in the Intergroup 0116 study, with nearly 90% of patients receiving at least D1 lymphadenectomy and a median of 20 lymph nodes removed. The 5-year OS was approximately 41% in both arms, and although these results appear to compare favorably to both the MAGIC and Intergroup 0116 trials, there was no evidence of superiority for either arm. Grade 3 hematologic toxicity was slightly higher in the perioperative chemotherapy arm (44% vs 34%), but patients in both arms had difficulty completing protocol treatment (47% for perioperative chemotherapy, 52% for adjuvant chemoradiotherapy). In light of these findings, we do not recommend adjuvant chemoradiotherapy for patients who undergo R0 resection following neoadjuvant ECF unless they are unable to tolerate multiagent chemotherapy in the postoperative setting or are enrolled in a clinical trial.

The role of chemoradiotherapy is less well defined for patients who undergo surgical resection with either positive margins or gross residual disease, because no prospective data exist to guide treatment decisions in this setting. However, a retrospective review including patients from the Dutch lymphadenectomy trial revealed both an LRR benefit (6% vs 26%) and an OS benefit (66% vs 29%) at 2 years following the addition of chemoradiotherapy to R1 resection. A subsequent population-level analysis of the Netherlands Cancer Registry confirmed these findings,[30,31] and a retrospective case series of patients who underwent adjuvant chemoradiotherapy noted equivalent OS and LRR in patients who underwent either R0 or R1 resection.[32] Furthermore, in a randomized trial examining neoadjuvant chemotherapy for patients with esophageal cancer, long-term survival following R1 resection was achieved only in patients who received adjuvant chemoradiotherapy.[33] Taken together, these data suggest that adjuvant chemoradiotherapy should be considered standard in patients with positive margins or gross residual disease, assuming that radiotherapy was not delivered preoperatively.

Role of Radiotherapy in the Neoadjuvant Setting

For many sites throughout the gastrointestinal tract, neoadjuvant or definitive chemoradiotherapy is gaining acceptance as an alternative to immediate surgical resection. In the United States, locally advanced rectal cancers and esophageal cancers are now routinely treated with neoadjuvant chemoradiotherapy following publication of the German Rectal and CROSS trials, respectively. Indeed, studies of esophageal cancer, which have typically included adenocarcinomas of the gastroesophageal junction and gastric cardia, may be particularly instructive when considering treatment for gastric malignancies. The POET trial randomized patients with Siewert Type I-III adenocarcinoma of the gastroesophageal junction to neoadjuvant chemotherapy or chemoradiotherapy.[34] Neoadjuvant chemotherapy consisted of cisplatin, leucovorin, and 5-FU in combination, while neoadjuvant chemoradiotherapy included this regimen followed by radiotherapy administered with concurrent cisplatin and etoposide. Although this trial was limited by poor accrual and ultimately closed early, there was a strong trend toward improved OS with the addition of radiotherapy to neoadjuvant treatment. Additionally, the pCR rate and node positivity rate were improved with chemoradiotherapy despite a dose of only 30 Gy. Longer-term follow-up of patients in this study, reported at the 2016 Annual Meeting of the American Society of Clinical Oncology, again noted an apparent OS advantage with chemoradiotherapy (39.5% vs 24.4% at 5 years), but these results failed to achieve statistical significance ($P = .055$).[35]

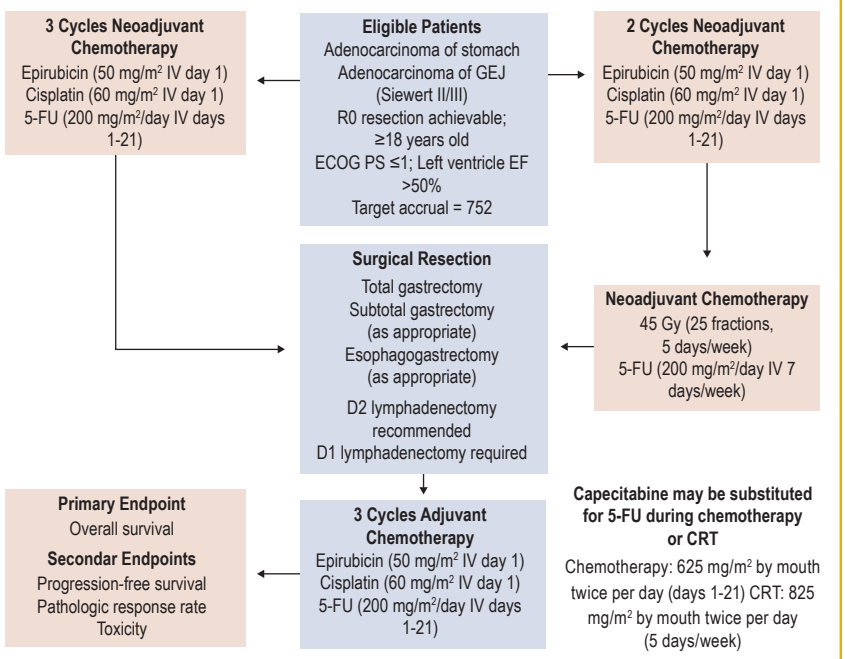
Neoadjuvant chemoradiotherapy confers several benefits relative to the postoperative setting, including smaller target volumes, improved patient compliance, and removal of the irradiated normal tissue at the time of resection, which may limit late-onset toxicity. The use of neoadjuvant, rather than adjuvant, chemoradiotherapy may not only be better tolerated by patients, but also be more oncologically efficacious. Retrospective data from The University of Texas MD Anderson Cancer Center have demonstrated the tolerability of this approach in patients with a minimum of T2N0 gastric cancer, and

TABLE: Major Randomized Trials of Chemoradiotherapy for Adenocarcinoma of the Stomach and Gastroesophageal Junction

Trial	Years	Patients: N, Stage, Location	Randomization	Primary Outcome	Comments
INT-0116[18,19]	1991-1998	556; Stage Ib+; Stomach/GEJ	1. Surgery 2. Surgery → CRT	Median OS 35 months 27 months	1. 85% pN+ 2. Majority D0/D1 LN dissection 3. Outdated RT techniques
MAGIC[24]	1994-2002	503; Stage II+; Stomach/GEJ	1. Surgery 2. ECF → Surgery ECF	5-year OS 23% 36%	1. 0% pCR rate 2. Poor treatment compliance (42%)
POET[34,35]	2000-2005	119; T3/T4 NX M0; Cardia/GEJ	1. PLF Surgery 2. PLF→CRT→Surgery	3-year OS 28% 47% (NSS)	1. Underpowered (closed early) 2. CRT: 30 Gy, concurrent EP
ARTIST[22]	2004-2008	458; Stage Ib+; Stomach/GEJ	1. Surgery (D2)→XP 2. Surgery (D2) → XP / CRT / XP	3-year DFS 74.2% 78.2% (NSS)	1. OS not analyzed 2. SS DFS benefit in pN-positive patients
CRITICS[29]	2007-2015	788; Stage Ib+; Stomach/GEJ	1. ECC → Surgery → ECC 2. ECC → Surgery →CRT	5-year OS 41.3% 40.9%	1. Abstract only 2. Poor treatment compliance (CT: 47%; CRT: 52%)
TOPGEAR[37]	2009-2017	752 (est); Stage Ib+; Stomach/GEJ	1. ECF →Surgery→ECF 2. ECF→CRT→Surgery ECF	5-year OS	1. Pending presentation/ publication 2. Accrual expected December 2017
ARTIST 2[23]	2013-2019	900 (est); pN positive; Stomach/GEJ	1. Surgery (D2)→S-1 2. Surgery (D2)→SOX 3. Surgery (D2)→SOX / CRT / SOX	3-year DFS	1. Pending presentation/ publication 2. Accrual expected 2019

5-FU indicates 5-fluorouracil; CRT, chemoradiotherapy; CT, chemotherapy; D2, extended systemic lymphadenectomy; DFS, disease-free survival; ECC, epirubicin, cisplatin, capecitabine; ECF, epirubicin, cisplatin, 5-FU; EP, etoposide, cisplatin; est, estimated; GEJ, gastroesophageal junction; Gy, gray (unit); LN, lymph node; NSS, not statistically significant; OS, overall survival; pCR, pathologic complete response; PLF, cisplatin, leucovorin, 5-FU; pN, pathologic N stage; RT, radiotherapy; S-1, an oral fluoropyrimidine; SOX, S-1, tegafur, gimeracil, and oteracil; SS, statistically significant; XP capecitabine, cisplatin.

FIGURE 1: TOPGEAR Trial Schema



5-FU indicates 5-fluorouracil; D1, limited; D2, extended; ECOG, Eastern Cooperative Oncology Group; EF, ejection fraction; GEJ, gastroesophageal junction; Gy, gray (unit); IV, intravenous; PS, performance status.

Adapted from reference 37.

80% of these patients ultimately underwent R0 resection with a 20% pCR rate.[36] Given this apparent benefit, the randomized phase III TOPGEAR study, which is expected to complete patient accrual in December 2019, was designed with the hope of elucidating the role of neoadjuvant chemoradiotherapy.[37] The investigational arm of this trial employs perioperative ECF as prescribed in the MAGIC trial, except chemoradiotherapy is substituted for the third neoadjuvant cycle of chemotherapy (**Figure 1**). Chemoradiotherapy, delivered concurrently with either continuously infused 5-FU or oral capecitabine, consists of a 45 Gy dose to the entire stomach, any perigastric tumor extension, and regional lymph nodes. A recently published interim analysis suggests similar rates of surgical complications and treatment compliance in the investigational and control arms of this trial, but oncologic outcomes are not yet available.[38] Final results from the TOPGEAR study should help clarify the role of radiotherapy in the setting of perioperative chemotherapy. A summary of several major randomized trials is available in the **Table.**

Role of Radiotherapy in Cases of Unresectable Gastric Cancer

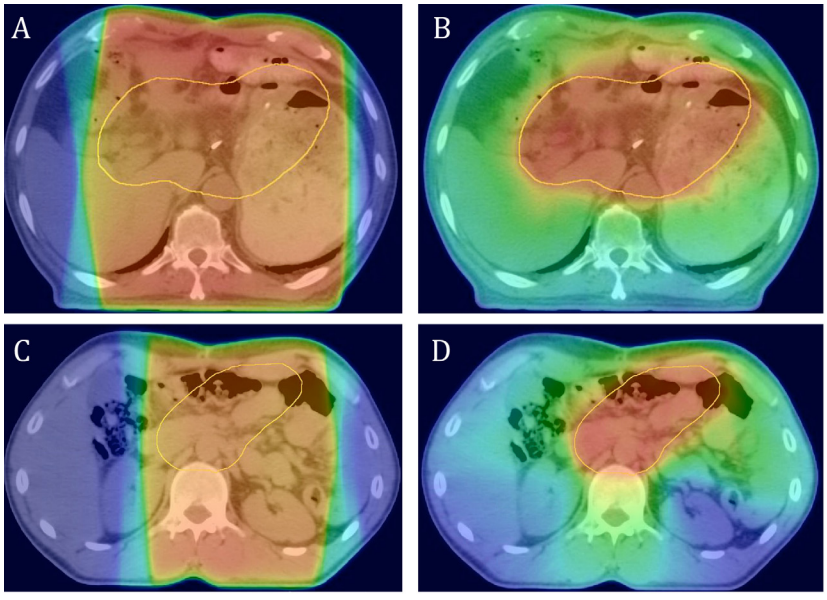
In contrast to data regarding patients with resectable gastric cancer, there are limited data to guide the treatment of patients with nonmetastatic, unresectable gastric cancers. Nonetheless, the available literature suggests that chemoradiotherapy may have a role in achieving durable palliation and conversion to resectable disease. In the midtwentieth century, randomized data demonstrated a clear survival benefit for patients with unresectable cancers of the stomach when 5-FU was added to palliative radiotherapy, although no patients were reported to have received an attempted curative resection.[39] More recently, a Japanese phase II study that employed chemoradiotherapy for patients with unresectable locally advanced gastric cancer demonstrated an eventual resection rate of 33.3% and an overall pCR rate of 13.3%.[40] In this study, 40 Gy in 2 Gy daily fractions were delivered to the primary tumor and regional lymph nodes with concurrent S-1 and cisplatin. The authors also reported that all 30 patients required hospitalization due to disease-related symptoms at the time of diagnosis; however, 97% were discharged after 1 cycle of chemotherapy, suggesting that even patients who did not reach surgery benefited from treatment.

An alternative approach to treatment of unresectable gastric cancer is multi-agent chemotherapy alone. Although a thorough discussion of this approach is beyond the scope of this review, many regimens can be used in this setting. However, in patients with good performance status and minimal comorbidity, we believe that incorporation of radiotherapy into gastric cancer treatment regimens could provide the highest likelihood of conversion to oncologic resectability and long-term disease control. Consequently, we recommend that such patients be evaluated in the multidisciplinary setting with appropriate input from surgeons, medical oncologists, and radiation oncologists with extensive experience in the treatment of gastric malignancies.

Radiotherapy Planning and Delivery

The Intergroup 0116 trial, which set the standard of care for adjuvant chemoradiotherapy, employed radiation techniques that are considered outdated in the modern radiation oncology clinic. Since the time of this trial, 3-dimensional conformal radiotherapy, image-guided radiotherapy (IGRT), IMRT, and volumetric modulated arc therapy (VMAT) have become commonplace in the United States. These techniques can achieve extensive normal tissue sparing with excellent target coverage (**Figure 2**). Without question, a minimum standard in the definitive setting should be CT-based simulation with 3-dimensional planning, given the large volumes typically employed and multiple radiosensitive organs at risk in near proximity to the target. Target delineation in gastric cancer is extremely complicated: even with the simple beam arrangements utilized in the Intergroup 0116 trial, approximately one-third of plans submitted for central review

FIGURE 2: Dosimetric Colorwash Comparison of Conventional Radiotherapy and Volumetric Modulated Arc Therapy (VMAT)



Two patients, each with resected pT3N3M0 adenocarcinoma of the stomach, were treated with 4500 centigray (cGy) in 180 cGy fractions prescribed to the planning target volume (yellow line) with concurrent capecitabine. Conventional plans (A,C) are shown in the left column; VMAT plans (B, D) are shown in the right column. There is substantial liver-sparing in the first patient (top row) and kidney-sparing in the second patient (bottom row) with VMAT.

were in violation of the prescribed protocol.[41] With the introduction of more conformal techniques and tighter margins, consideration and knowledge of anatomical patterns of spread is crucial.

Prior to initiation of radiotherapy, appropriate imaging and work-up are crucial to guide the treatment planning process. All patients with gastric cancer should undergo esophagogastroduodenoscopy and biopsy of the primary tumor, as well as endoscopic ultrasound to determine depth of invasion and to assess regional lymph nodes. A CT scan of the chest, abdomen, and pelvis, with both oral and intravenous contrast, is critical to assess regional lymphadenopathy and rule out metastatic disease. Although PET is not as sensitive in detection of lymph node and distant metastases secondary to limited 18F-deoxyglucose avidity in certain histologic subtypes, the use of combined PET/CT is now recommended by the National Comprehensive Cancer Network[42] and may be useful for radiotherapy target delineation. A full discussion of laparoscopic staging with peritoneal cytology is beyond the scope of this review, but its use may be appropriate in patients for whom neoadjuvant therapy is planned.

Before CT simulation and each radiotherapy fraction, patients should fast for several hours in order to maximize reproducibility of gastric filling. Patients are typically positioned supine, with arms immobilized above the head to allow multifield or volumetric modulated arc therapy plans. The use of a custom immobilization device is recommended to minimize set-up uncertainties, and intravenous contrast is essential for the proper delineation of lymphatic target volumes. We recommend obtaining the simulation CT with and without oral contrast for optimal treatment planning, as well as contouring of the primary tumor or resection bed. Motion management strategies, which may include 4-D CT, respiratory gating, or abdominal compression, should be considered because target volumes are susceptible to substantial respiratory movement. Finally, for patients who have undergone surgical resection, fusion of available preoperative imaging is essential, as is thorough review of the operative note and surgical pathology. Target delineation in both the neoadjuvant and adjuvant setting is complicated, requiring a detailed understanding of regional lymphatic spread patterns and postoperative anatomy. Furthermore, these volumes may vary significantly depending on the location of the primary tumor and extent of surgical resection, if performed.

In the majority of patients, target volumes will include the primary tumor or resection bed, gastric remnant (if present), and regional lymph nodes; however, in some patients, inclusion of the duodenal stump or surgical anastomosis may be advisable.[41] Given the results of the Intergroup 0116 trial, 45 Gy given in 25 daily fractions is considered standard, but a boost of 5.4 to 9 Gy may be given for positive margins, gross residual disease, or definitive treatments. An excellent contouring atlas, published by Wo and colleagues in 2013, is available and highly useful for target delineation,[43] as is an additional guide that is specifically tailored to patients treated with D2 lymphadenectomy.[44] Organs at risk, including the kidneys, liver, small bowel, lungs, heart, and spinal cord, should be contoured and appropriately constrained. Given the high anatomic variability of this region, we recommend an IGRT technique if highly conformal methods such as IMRT are employed.

Future Directions and Conclusions

Although substantial improvements in the management of gastric cancer have been made over the past several decades, overall outcomes remain disappointing with unsatisfactory cure rates in all but the earliest-stage patients. The optimal treatment paradigm for most patients with gastric cancer remains unclear and may vary with tumor histology and location. Furthermore, it appears that the traditional pillars of oncology are approaching their limits, and that future innovations are sorely needed. Targeted agents, novel radiosensitizers, and even new modalities may be necessary to improve upon the successes of the past half-century. However, radiotherapy continues to play a crucial role for many patients, particularly those who did not receive

preoperative therapy, are found to have positive lymph nodes, retain residual disease following surgery, or are unresectable at diagnosis. The role of a trimodality approach in the neoadjuvant setting is promising, but its use is still investigational.

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Case Study—Pathologic Complete Response Following a Single Cycle of Neoadjuvant Chemotherapy

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Abstract

BACKGROUND: Pathologic complete response (pCR) describes the absence of residual cancer on pathologic evaluation following systemic neoadjuvant therapy. The original goal of neoadjuvant therapy in breast cancer treatment was to decrease the tumor size for improved breast conservation and allow for evaluation of tumor susceptibility to specific treatments.

As neoadjuvant therapies have become more effective in decreasing cancer burden, pCR has become an attainable endpoint for breast cancer treatment. Several studies suggest pCR rates in estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and human epidermal growth factor receptor 2 (HER2)-positive breast cancers after a regimen of neoadjuvant TCH+P (docetaxel [T], carboplatin [C], trastuzumab [H], pertuzumab [P]) are between 57-66%.

METHODS: A case of pCR after a single cycle of neoadjuvant chemotherapy was reviewed. Clinical, surgical, and pathologic details were collected by chart review to outline treatment regimen and response. Background, current national guidelines, and relevant papers were collected using PubMed.

RESULTS: A 64-year-old female complained of an enlarging left breast mass. Reactive oxygen species (ROS) was unremarkable and physical exam revealed a 1.5cm non-fixed mass in the inferior breast without skin changes, nipple discharge, or palpable lymphadenopathy.

Subsequent imaging noted a 1.4 × 1.2 × 1.2 cm lesion on ultrasound and 5.0 × 5.0 cm mass on mammogram.

Ultrasound-guided core biopsy yielded grade II infiltrating ductal carcinoma (IDCA) with ER-negative, PR-negative, HER2 3-positive immunostaining. Metastatic workup was negative. The multidisciplinary treatment team decided on neoadjuvant therapy with TCH+P.

Cycle #1 was complicated with 3 hospitalizations for nausea, vomiting, diarrhea, dehydration, and diabetic ketoacidosis. She refused further treatment and opted for surgical intervention and adjuvant chemotherapy to follow. Physical exam revealed no palpable mass at this time.

Surgery was uncomplicated and pathology revealed no residual sign of carcinoma with a pathologic stage of ypT0ypN0(sn)cM0 (yp representing post-neoadjuvant treatment; sn representing sentinel node; c representing clinical) with a pCR after 1 round of TCH+P.

CONCLUSION: A pCR of HER2-positive IDCA of the breast following a single cycle of neoadjuvant chemotherapy suggests that research into fewer than the current standard number of cycles of neoadjuvant therapy may help define the optimal treatment to obtain pCR in HER2-positive breast cancer. Fewer cycles would decrease toxicity, adverse events, and financial stress to patients with cancer. We are excited about the future possibilities of research advancement in this area and encourage a randomized prospective multicenter clinical trial exploring this idea.

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Introduction

Pathologic complete response (pCR) is a term used to describe the absence of residual cancer on pathologic evaluation following systemic neoadjuvant therapy. The original goals of neoadjuvant therapy in breast cancer treatment were to:

1. Decrease tumor size for improved breast conservation rates and decreased axillary surgery.
2. Allow for evaluation of tumor susceptibility to specific treatments.

As neoadjuvant therapies have proved their ability to eradicate disease in the breast and lymph nodes, pCR has become an attainable endpoint for breast cancer treatment in some patients.

There is a high rate of pCR in human epidermal growth factor receptor 2 (HER2)-positive, hormone receptor (HR)-negative breast cancers treated with neoadjuvant TCH+P (docetaxel [T], carboplatin [C], trastuzumab [H], pertuzumab [P]). The regimen involves 6 cycles of chemotherapy followed by surgery and radiation therapy (RT), if indicated, with trastuzumab therapy continuing for 1 year.

In the literature, pCR has been described to occur following complete neoadjuvant treatment regimens; however, it is not unusual for the protocol to be aborted due to toxic adverse events (AEs). We present 1 case in which overwhelming AEs limited TCH+P to a single cycle, yet resulted in a pCR of a grade II invasive ductal carcinoma.

Methods

Case Presentation

A 64-year-old female with a past medical history significant for endometrial cancer (stage II, status: post total abdominal hysterectomy and bilateral salpingo-oophorectomy with 3 rounds of carboplatin/paclitaxel with RT) in remission since 2013, diabetes, fibromyalgia, spinal fusion, osteoarthritis, and psoriasis presented in January 2016 to Rush University Medical Center Breast Surgery clinic complaining of an enlarging left breast mass.

Review of systems was unremarkable except for the left-breast mass. Physical exam of the left breast revealed a 1.5-cm mobile mass in the 6:00 position, 2.5 cm from the nipple, without skin changes or nipple discharge. There was no palpable lymphadenopathy.

She underwent a subsequent mammogram and ultrasound. On mammogram, the area of abnormality spanned 5 cm. A core biopsy of the mass revealed a poorly differentiated infiltrating ductal carcinoma, grade II. Immunostaining showed the cancer was estrogen-receptor weakly positive (5%), progesterone-receptor 0%, and HER2-positive (3+).

MRI was recommended for further evaluation of the extent of the malignancy since the physical exam and mammogram were discordant; however, the patient was unable to have the MRI performed. CT scans of the chest, abdomen, and pelvis were performed, along with a bone scan, and all were negative for metastatic disease.

The presence of HER2-positive disease made our patient a promising candidate for neoadjuvant chemotherapy with TCH+P. The initial multidisciplinary plan was for TCH+P x 6 cycles, followed by lumpectomy and sentinel lymph node (SLN) biopsy, followed by radiation therapy, with trastuzumab to continue for 1 year.

Cycle 1 of chemotherapy was poorly tolerated with 3 hospitalizations for severe nausea, vomiting, diarrhea, dehydration, and diabetic ketoacidosis. The patient also developed a disseminated rash requiring dermatology consultation. Our patient's previous carboplatin/paclitaxel for her endometrial cancer 3 years prior may have contributed to her poor tolerance of TCH+P. Due to these complications, she refused further treatment and was referred for surgical intervention at this time with plans for adjuvant chemotherapy to follow. Physical exam revealed no palpable mass in the breast and a clinically negative axilla.

The multidisciplinary tumor board reviewed her case and agreed her cancer could be appropriately treated with breast conservation therapy (BCT) as opposed to a total mastectomy. BCT is performed in 3 steps: 1) surgical removal of the tumor itself, achieving a pathologically free margin of excision; 2) surgical staging of the axilla either by way of SLN biopsy or axillary dissection; 3) RT to the breast and a portion or all of the regional lymph nodes.

Our patient underwent an uncomplicated left wire-directed segmental mastectomy with SLN biopsy.

Specimen imaging confirmed an intact wire, biopsy clip, and lesion of interest. The pathologic specimen labeled left breast partial mastectomy tissue was an ill-defined white, firm, fibrous area measuring 6 × 7.5 × 1.5 cm associated with focal hemorrhage that corresponded with radiologic calcifications. Evaluation revealed histiocytic reaction, chronic inflammation, fibrosis, and calcifications that were consistent with therapy effect. No residual carcinoma was identified (**Figure**).

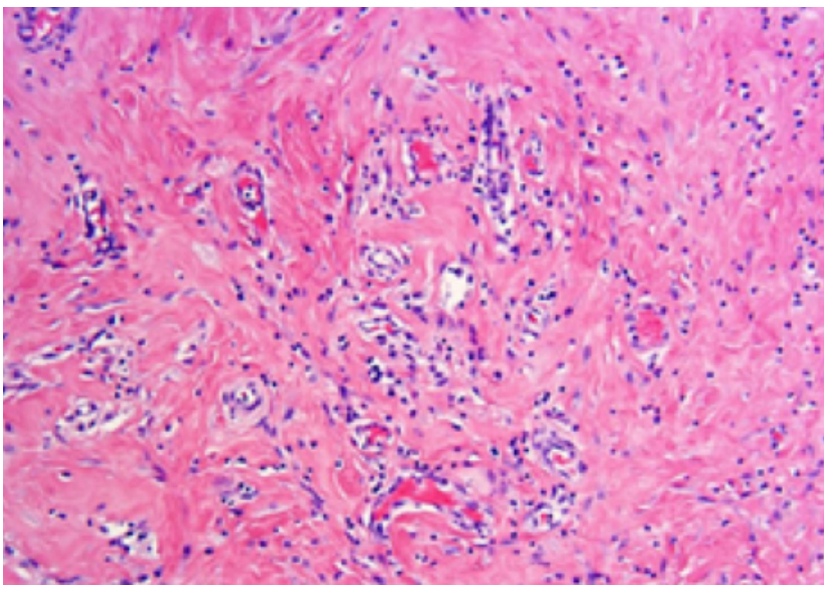
The specimen labeled left axilla sentinel lymph node was fibroadipose and lymphoid tissue measuring 2.0 × 2.0 × 0.7 cm. The node was negative for carcinoma.

Her final breast cancer staging based off of the American Joint Committee on Cancer was ypT0ypN0(sn)cM0 (yp representing postneoadjuvant treatment; sn representing sentinel node; c representing clinical) with a pCR after 1 round of TCH+P.[1]

Discussion

The FDA funded Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) meta-analysis by Cortazar and colleagues suggests several key features of pCR (defined in the study as ypT is, where is represents in situ):

FIGURE: Pathologic Complete Response.



The tumor bed shows therapy-associated changes including myofibroblasts, histiocytes, and inflammatory cells infiltrate. No residual tumor is seen.

1. Frequency of pCR is decreased in low-grade HR-positive tumors
2. Frequency of pCR is highest in HER2-positive, HR-negative aggressive tumors
3. Frequency of pCR is lowest in HER2-positive, HR-positive tumors.

Attaining pCR, regardless of receptor status, is associated with an increased event-free survival (EFS) of 0.25 (95% CI, 0.18-0.34) and overall survival (OS) of 0.19 (95% CI, 0.12-0.31). The study also notes a greater association with EFS and OS in the eradication of tumors from both the breast and lymph nodes versus eradication from breast tissue alone. Results of the large pooled CTNeoBC analysis also demonstrated that the strength of long-term correlation between pCR and survival is increased by the addition of trastuzumab to the therapy regimen.[2]

In a thorough analysis of pCR in association with the molecular subtypes of breast cancer, Wang-Lopez and colleagues concluded that pCR functions as a surrogate marker of survival for patients with HER2-positive breast cancer.[3] Numerous other reports have also suggested improvement in long-term survival in patients who attain pCR.[4-8] This relationship has gained significant support, so much so that the FDA released a "Guidance for Industry" collection of recommendations, the purpose of which is to encourage the use of pCR as an endpoint to support accelerated approval of trial designs. This guidance was prepared in conjunction with the FDA's Breast and Gynecological Oncology Group, Office of Hematology and Oncology Products, and Center for Drug Evaluation and Research.[9]

The neoadjuvant TCH+P regimen has been shown to have a pCR rate between 53% to 69% in HER2-positive, HR-negative cancers, according to the TRYPHAENA study. The primary outcomes of the study were focused on certain neoadjuvant chemotherapy regimens and their AEs, particularly looking at cardiotoxicity for trastuzumab.[10] The pCR of neoadjuvant regimens involving trastuzumab has been a focus of several well-regarded studies, including NOAH, CLEOPATRA, and NeoALTTO, which all show similar improved results.[11-13] Despite its high success rates for disease eradication, however, TCH+P can have significant toxic AEs for the patient.

AEs often lead to the abortion of neoadjuvant protocols. The TRYPHAENA study revealed TCH+P's significant AEs: Diarrhea, alopecia, and nausea were reported in >50% of patients. More than 35.5% of patients receiving TCH+P experienced serious AEs, including severe diarrhea, vomiting, and febrile neutropenia. Such effects were witnessed in our patient; she developed severe nausea and diarrhea resulting in multiple hospitalizations for diabetic ketoacidosis, and ultimately in the discontinuation of treatment.[10]

The primary outcome of the TRYPHAENA study was to assess the tolerability and safety of pertuzumab and trastuzumab given in combination with anthracycline-containing neoadjuvant chemotherapy for HER2-positive breast cancer. This AE was measured using left ventricular ejection fraction. Incidence of systolic dysfunction was found to be low, and secondary findings of increased pCR rates when trastuzumab was added to the regimen further supported its addition to chemotherapy regimens.[10] Recent studies confirm that the risk of cardiac toxicity is actually significantly lower in trastuzumab patients than was previously suspected (<6%).[14]

Studies on the efficacy of reducing the number of neoadjuvant cycles for breast cancer have not been widely published. This case report supports the funding of research to determine the optimum number of TCH-P cycles in HER2-positive neoadjuvant chemotherapy. Of interest, a large 2012 study on the reduction of adjuvant chemotherapy cycles identified no additional benefit of 6 versus 4 cycles of chemotherapy for certain breast cancers. The prospective study randomly assigned 3171 patients to either 4 or 6 cycles of therapy with an average follow-up of 5.3 years. The primary efficacy endpoint was measured as relapse-free survival.[15]

While this case report cannot independently suggest that fewer cycles of standard neoadjuvant chemotherapy should be used to attain pCR in HER2-positive breast cancers, it is important to document that such examples exist. To further understand the significance of this finding, a prospective multi-institution trial could be performed to randomize patients into treatment groups with varying numbers of neoadjuvant cycles, measure pCR rates per group, and correlate number of cycles with pCR rate. Long-term follow-up measuring disease-free and overall survival rates would be necessary to evaluate if treatment regimens that include decreased cycles of neoadjuvant chemotherapy are a possibility.

Conclusion

In summary, this is the first documented case of pCR following a single cycle of neoadjuvant chemotherapy for HER2-positive breast cancer. Studies suggest that pCR can be used as a surrogate marker for survival in HER2-positive breast cancers.[3] Of note, some studies have shown that a reduction of adjuvant chemotherapy cycles is not inferior to standard treatment for certain breast cancers.[15]

This report suggests that research into fewer than the current standard number of cycles of neoadjuvant therapy may help define the optimal treatment to obtain pCR in HER2-positive breast cancer. We are excited about the future possibilities of research advancement in this area and encourage a randomized prospective multicenter clinical trial exploring this idea.

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Immunotherapy for Triple-Negative Breast Cancer: A Focus on Immune Checkpoint Inhibitors

Isha Dua, MD, and Antoinette R. Tan, MD, MHSc

Abstract

Triple-negative breast cancer (TNBC) is a clinically heterogeneous and molecularly diverse disease. At present, chemotherapy is the standard treatment for early-stage and metastatic TNBC. The paucity of actionable targets, lack of targeted therapies, and relatively poor prognosis of patients with TNBC have created ample opportunity to evaluate novel treatment approaches. An improved understanding of the immunogenicity of TNBC has led to clinical studies of several immunotherapeutic agents. Early phase I trials with immune checkpoint inhibitors in TNBC report an overall response rate of up to 19% with durable clinical responses and a tolerable safety profile. The hope is that immunotherapy strategies will provide new therapeutic options for TNBC. This review focuses on the emerging data about immune checkpoint inhibitors in the treatment of TNBC.

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Introduction

Triple-negative breast cancer (TNBC) is clinically defined as breast tumors lacking expression of estrogen receptor (ER) and progesterone receptor, with normal human epidermal growth factor receptor type 2 *(HER2)* gene copy number and expression.[1] It accounts for approximately 15% to 20% of all breast cancers and is more prevalent in younger women and in African-American women.[2] TNBC has an aggressive natural history, with an increased mortality rate during the first 5 years with most deaths occurring in the first 5 years.[3] Typically, there is a high risk of early recurrence and this tends to occur within the first 4 years after diagnosis. Compared with other subtypes, visceral metastasis is more likely, involving the brain and lungs.[4]

TNBC is also characterized by molecular heterogeneity. There is diversity in the histologic patterns and transcriptional subtypes. The majority of TNBCs are high-grade invasive ductal carcinomas, but there is a small subset with distinct pathology and indolent biologic behavior, such as adenoid cystic carcinoma.[5] Lehmann and colleagues proposed a classification that defined several molecular subtypes of TNBC; these include 2 basal-like (BL1 and BL2), an immunomodulatory, a mesenchymal, a mesenchymal stem-like, and a luminal androgen receptor subtype.[6] Similarly, another gene expression analysis suggested the following subgroups: luminal/androgen receptor, mesenchymal, BL/immune-suppressed, and BL/immune-activated.[7] These classifications help to increase our understanding of the biology of TNBC and identify rational therapeutic strategies for TNBC subtypes.

Chemotherapy is the current standard-of-care treatment of TNBC in the adjuvant, neoadjuvant, and metastatic settings. TNBCs are highly sensitive to chemotherapy, as evidenced by pathologic complete response (pCR) rates in the 30% to 40% range after neoadjuvant chemotherapy, compared with complete response (CR) rates for ER-positive breast cancer, which range from 10% to 25%. However, TNBC has higher rates of relapse, which has been referred to as the triple-negative paradox.[8-10] The need to improve the outcomes of patients with TNBC drives large-scale clinical investigational efforts to evaluate novel therapeutic approaches. Immunotherapy, such as checkpoint inhibitors, represents a modality that has changed the treatment landscape for other solid tumors, especially melanoma and non–small cell lung cancer (NSCLC). The potential role of immune checkpoint blockade therapy in TNBC is the focus of this review.

Rationale for Immunotherapy in Triple-Negative Breast Cancer

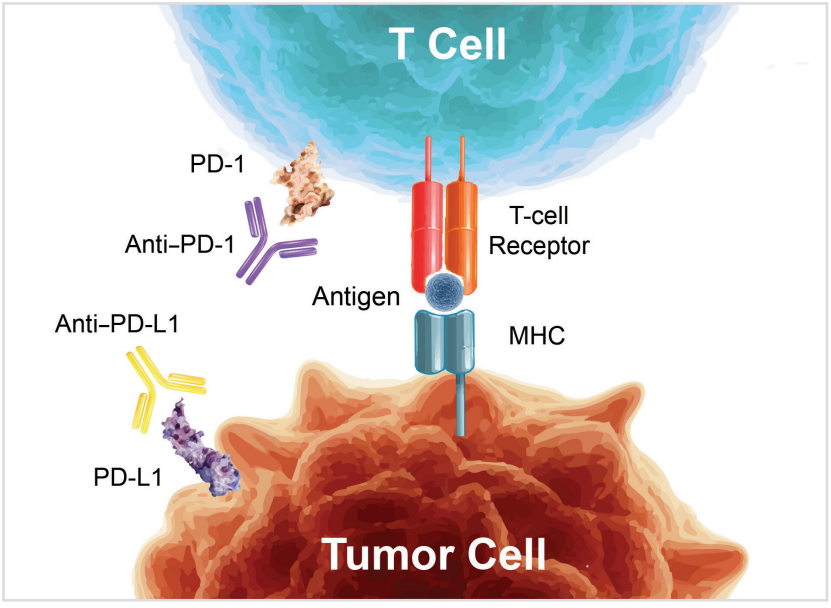
Breast cancer is not traditionally considered an immunogenic tumor. Available literature suggests that it is reasonable to investigate therapies that target programmed death-1/programmed death ligand-1 (PD-1/PD-L1) in TNBC. PD-1 is a checkpoint receptor expressed primarily by activated T cells, and it limits T-cell effector functions. PD-L1, a T-cell inhibitory molecule, is expressed on cancer cells, tumor-infiltrating inflammatory cells, and immune cells. The binding of PD-L1 to PD-1 on T cells is a major mechanism of tumor immune evasion (**Figure**). Mittendorf and colleagues reported higher expression of PD-L1 in TNBC than in hormone receptor (HR)-positive breast cancers.[11] The analysis on tissue microarrays showed that 19% of 105 primary TNBC specimens were PD-L1 positive.

In addition, Tung and colleagues found that 26% of primary TNBCs (51 of 193) expressed PD-L1 on the surface of the cancer

cells,[12] although the role of PD-L1 as a biomarker is unclear. Based on the current clinical studies described later, it may not be completely predictive of treatment response. Additionally, there is variability in the methodologies to assess PD-L1 expression, in the different numerical cut-off values for positivity, and in the analysis being performed on different types of tissue, which include archived, fresh, primary, and metastatic specimens.

The presence of tumor-infiltrating lymphocytes (TILs) suggests an immune response to tumor-associated antigens. Several studies have evaluated TILs in breast cancer specimens and a higher level of TILs has been reported in TNBCs compared with HR-positive breast cancers.[13] Also, available data indicate that TILs have prognostic significance in TNBC.[14,15] Furthermore, TNBC is characterized by genomic instability and high rates of genetic mutations, which implicate production of more neoantigens and increased immunogenicity.[16,17] The tumor mutational load is higher in TNBC compared with other subtypes.[18] Taken together, there is strong rationale to therapeutically target TNBC with monoclonal antibodies that block the PD-1/PD-L1 axis. Findings from some of the early phase I clinical trials with checkpoint inhibitors that enrolled patients with metastatic TNBC will be discussed (**Table**).

FIGURE. Immune Checkpoint Blockade



MHC indicates major histocompatability complex. A major checkpoint, mediated by the interaction between PD-1 on T cells and its ligand, PD-L1, on tumor cells, has been the focus of many clinical trials. Immune checkpoint blockade has changed the treatment landscape of several solid tumors. Source: Drake CG, Lipson EJ, Brahmer JR. Breathing new life into immunotherapy: review of melanoma, lung and kidney cancer.
Source: *Nat Rev Clin Oncol.* 2014 Jan;11(1):24-37.

TABLE. Select Clinical Trial Results of Checkpoint Inhibitors in Metastatic Triple-Negative Breast Cancer

Trial	Phase	Agents	Evaluable Subjects for Response	PD-L1 Status	Endpoints
KEYNOTE-012, NCT01848834	Ib	Pembrolizumab	27 TNBC	PD-L1 expression in stroma or in ≥ 1% of tumor cells	ORR: 18.5% 1 CR, 4 PRs, and 7 SD 6-month PFS: 24.4%
GO27831, NCT01375842	I	Atezolizumab	21 TNBC	PD-L1 ≥ 5% on tumor-infiltrating immune cells	ORR: 19% 2 CRs, 2 PRs 6-month PFS: 27%
JAVELIN, NCT01772004	Ib	Avelumab	168 58 TNBC	Unselected	In the overall group: ORR: 4.8% 1 CR, 7 PRs, and 39 SD In TNBC: ORR: 8.6% 5 PR and 13 SD
GP28328, NCT01633970	Ib	Atezolizumab and nab-paclitaxel	32 TNBC	Unselected	ORR: 38% 3% CR, 34% PR, 44% SD

CR indicates complete response; ORR, overall response rate; PD-L1, programmed cell death ligand; PFS, progression-free survival; PR, partial response; SD, stable disease; TNBC, triple-negative breast cancer.

PD-1 Inhibitors

Nivolumab and pembrolizumab are PD-1–targeting antibodies that are approved by the FDA. Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody directed against PD-1, and it is indicated in the treatment of several cancers, including wild-type *BRAF* and mutant *BRAF* metastatic melanoma; previously treated metastatic NSCLC; advanced renal cell cancer after prior antiangiogenic therapy; recurrent or metastatic squamous cell carcinoma of the head and neck on or after platinum-based therapy; previously treated locally advanced or metastatic urothelial carcinoma progressed during or following platinum-based chemotherapy; and relapsed or progressed classical Hodgkin lymphoma after auto-hematopoietic stem cell transplant and posttransplantation brentuximab vedotin.[19-28]

Several phase I and II trials are being conducted with nivolumab in TNBC. Nivolumab is currently being studied in an adaptive phase II trial of metastatic TNBC in which it is being given as monotherapy after induction treatment with various agents, including radiation, low-dose doxorubicin, metronomic

cyclophosphamide, and cisplatin (NCT02499367). Nivolumab is also being evaluated in combination with TAK-659, an inhibitor of spleen tyrosine kinase, in a phase Ib study of solid tumors with a dose expansion in metastatic TNBC (NCT02834247).

Pembrolizumab is a humanized monoclonal antibody of the IgG4 isotype that binds to PD-1 and blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab was approved by the FDA in several solid tumors including metastatic melanoma; in combination with pemetrexed plus carboplatin as a frontline treatment for patients with metastatic or advanced nonsquamous non–small cell lung cancer (NSCLC); untreated metastatic NSCLC whose tumors have high PD-L1 expression and no EGFR or anaplastic lymphoma kinase aberrations; metastatic NSCLC whose tumors express PD-L1 after disease progression on or after platinum-containing chemotherapy; and recurrent or metastatic head and neck squamous cell cancer with disease progression on or after platinum-containing chemotherapy.[29-32] Pembrolizumab was also granted accelerated approval for refractory classical Hodgkin lymphoma in adult and pediatric patients who have relapsed after 3 or more lines of therapy.[33]

KEYNOTE-012 (NCT01848834) was a multicohort, nonrandomized phase 1b basket trial that enrolled multiple subpopulations of tumors including metastatic TNBC, advanced head and neck cancer, advanced urothelial cancer, and advanced gastric cancer. Nanda and colleagues reported the results of the first single-agent anti-PD-1 therapy in the metastatic TNBC cohort within KEYNOTE-012.[34] This trial screened 111 metastatic TNBC patients for PD-L1 positivity, defined as staining in the stroma or in ≥1% of tumor cells assessed immunohistochemically using a 22C3 antihuman PD-1 antibody. Of of the 65 patients (58.6%) with tumors that were PD-L1–positive, 32 patients were treated with pembrolizumab 10 mg/kg intravenously (IV) every 2 weeks. About 50% of patients had at least 3 prior regimens for metastatic disease; 25% of patients received 5 or more previous lines. The median number of prior therapies for metastatic disease was 2 (range, 0-9). Most patients (87.5%) had previous neoadjuvant or adjuvant therapy. All patients had prior taxane exposure and 72% had prior anthracyclines.

The overall response rate (ORR) based on central review assessed by RECIST v1.1 in 27 evaluable patients was 18.5% (95% CI, 6.3-38.1); 1 (3.7%) patient had a CR; 4 (14.8%) partial responses (PRs) were observed; and 7 (25.9%) patients had stable disease. Median time to response was 17.9 weeks (range, 7.3-32.4 weeks). Median duration of stable disease was 17.0 weeks (range, 7.1 weeks-32.1 weeks). Additionally, the 6-month progression-free survival (PFS) rate was 24.4%. At the time of the publication, the median duration of response had not been reached (range, 15.0 to ≥47.3 weeks), and 3 responders had received treatment for ≥1 year. An updated status of the responders in this metastatic TNBC cohort was presented at the 2016 San Antonio Breast Cancer Symposium.[35] Median PFS was 1.9 months (95% CI, 1.3 months-4.3 months) and median overall survival (OS) was 10.2 months (95% CI, 5.3-17.5). Of the 5 responses, 3 have been described as long-lasting. The TNBC patient who experienced a CR, who had previously been treated with 8 lines of chemotherapy for metastatic disease, discontinued pembrolizumab 11 months after achieving a CR and was in a CR for an additional 15 months after treatment was stopped. Two of the patients with a PR discontinued pembrolizumab after 2 years of treatment; 1 patient has maintained response for 22.7 months and the other patient experienced disease progression after 7.7 months and restarted the pembrolizumab per protocol, which led to stable disease.

The most common adverse events (AEs) of any grade related to pembrolizumab were arthralgia (18.8%), fatigue (18.8%), myalgia (18.8%), nausea (15.6%), and diarrhea (12.5%). There was 1 grade 5 disseminated intravascular coagulation felt to be treatment-related. Immune-related AEs included grade 2 hypothyroidism, grade 3 colitis, and grade 3 hepatitis (1 of each).

To test the efficacy of pembrolizumab as monotherapy in a trial appropriately powered to assess response, a phase II, 2-part, multisite, open-label trial (KEYNOTE-086; NCT02447003) in metastatic TNBC was designed. Part 1 included 2 cohorts for enrollment. Cohort A enrolled patients with centrally confirmed metastatic TNBC who had received at least 1 systemic treatment for metastatic disease and documented disease progression on the most recent therapy. Participants must have been previously treated with an anthracycline and a taxane in the neoadjuvant, adjuvant or metastatic setting. Cohort B enrolled subjects with centrally confirmed PD-L1–positive metastatic TNBC who had not received any prior systemic treatment for metastases. Part 2 is an expansion of cohort A that will enroll patients with tumors strongly positive for PD-L1 expression; part 2 will be initiated only if ≥1 response is observed in the cohort A PD-L1–strong-positive population. In all cohorts, patients will receive pembrolizumab 200 mg IV every 3 weeks until disease progression, intolerable toxicity, or patient or investigator decision. The primary outcome measure is ORR. This trial has completed accrual.

Several phase III trials are currently underway or planned which will further evaluate the role of pembrolizumab monotherapy in the treatment of TNBC. A phase III study (KEYNOTE-119; NCT02555657) is testing the activity of single-agent pembrolizumab versus chemotherapy of physician's choice as second- or third-line treatment for metastatic TNBC. Eligible subjects must have centrally confirmed TNBC, have received 1 or 2 prior chemotherapy treatments for metastatic disease, have documented progression on most recent therapy, and have been previously treated with an anthracycline and/or a taxane. Randomization is 1:1 to pembrolizumab or single-agent chemotherapy chosen by the investigator, which includes capecitabine, eribulin, gemcitabine, or vinorelbine. The primary outcome measures are OS and PFS, and the accrual goal is 600 patients.

It is observed that patients with TNBC who achieve a pCR after neoadjuvant chemotherapy have excellent survival, and those who

have residual disease are at high risk for recurrence.[9] Several clinical trials have been designed to evaluate the role of further adjuvant therapy in patients with TNBC who have residual disease, since the presence of residual disease after neoadjuvant treatment predicts a poor prognosis. One example is a large randomized trial evaluating adjuvant pembrolizumab in early-stage TNBC. This phase III trial (SWOG-S1418, BR006; NCT02954874) will evaluate the effect of adjuvant treatment with pembrolizumab in 1000 patients with TNBC who have completed definitive local treatment. This is a collaborative effort led by Southwest Oncology Group and NRG Oncology, sponsored by the National Cancer Institute. Randomization is 1:1 to either 12 months of treatment with pembrolizumab or observation. Eligible patients are those who did not achieve a pCR following at least 16 to 24 weeks of neoadjuvant chemotherapy followed by surgery, with residual tumor ≥1 cm and/or axillary-node–positive disease. The primary endpoint is invasive disease-free survival (DFS). This is a very large trial with the potential to change the current adjuvant standard of care for TNBC patients with residual disease after neoadjuvant chemotherapy.

PD-L1 Inhibitors

Several PD-L1 inhibitors are in clinical development and include atezolizumab, avelumab, and durvalumab. Atezolizumab is an engineered monoclonal antibody of the IgG1 isotype that binds selectively to PD-L1 on immune cells or tumor cells to prevent interactions with the PD-1 receptor or B7-1 (CD80). Both interactions provide inhibitory signals to T cells. Atezolizumab is approved by the FDA for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy; or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; or in patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy, regardless of PD-L1 status.[36-38]

The safety of atezolizumab was assessed in a phase I study that enrolled patients with metastatic solid tumors (NCT01375842).[39] Fifty-four patients with metastatic TNBC were enrolled in this multidisease basket trial. The initial cohort enrolled only PD-L1–positive tumors, and this was later changed to all patients. Atezolizumab was given IV at 15 mg/kg, 20 mg/kg, or fixed dose of 1200 mg every 3 weeks. PD-L1 expression was assessed on tumor-infiltrating immune cells (ICs) using a proprietary immunohistochemical (IHC) SP142 antibody assay. PD-L1 positivity was defined as IHC IC3 (≥10% ICs PD-L1–positive) or IHC IC 2 (≥5% to <10% of ICs PD-L1–positive). Most patients (89%) had received 4 or more previous systemic regimens, including adjuvant, neoadjuvant and metastatic treatments. Similar to the pembrolizumab phase I study, the ORR was 19% (4 of 21 evaluable; 95% CI, 5-42), including 2 CRs and 2 PRs, and all these patients' tumors met PD-L1 positivity of ≥5%. Of note, 3 patients experienced pseudoprogression, or the appearance of new lesions that subsequently resolve in the context of a continued decrease in tumor burden. Three patients experienced stable disease. At the time of the presentation, the median duration of response had not been reached (range 18 to >56 weeks).

The 6-month PFS was 27% (95% CI, 7-47). The most common all-grade AEs in ≥3 patients were fatigue (15%), fever (15%), and nausea (15%). There was 1 case of grade 4 pneumonitis.

Another PD-L1 inhibitor undergoing clinical development is avelumab, which is a fully human IgG1 monoclonal antibody that binds to PD-L1. In May 2017, the FDA granted an accelerated approval to the agent in patients with locally advanced or metastatic urothelial carcinoma. Prior to that, the agency granted accelerated approval to avelumab for the treatment of adult and pediatric patients 12 years and older with metastatic Merkel cell carcinoma.[40] In a phase Ib solid tumor trial (JAVELIN; NCT01772004), there was a metastatic breast cancer cohort expansion of 168 patients, unselected for PD-L1 status and breast cancer subtype, treated with avelumab at 10 mg/kg IV every 2 weeks until progression.[41] The median number of prior therapies for metastatic disease in the overall population was 3 (range, 0-10). The ORR in the overall population (n = 168) was 4.8% (95% CI, 2.1-9.2) with 1 CR and 7 PRs; 39 (23.3%) patients had stable disease. At the time of the presentation, the median duration of response was 28.7 weeks (95% CI, 6.1 to not estimable). The TNBC subtype composed about 34.5% (n = 58) of subjects. About 50% of the TNBC patients had ≤1 prior regimen for metastatic disease. The ORR in the TNBC cohort was 8.6% (95% CI, 2.9-19); 5 of 58 patients had a PR, and 13 had stable disease (22.4%). For the other subtypes, the ORR was 3.8% in HER2-positive (95% CI, 0.1-19.6), and 2.8% (95% CI, 0.3-9.7) in HR-positive/HER2-negative.

PD-L1 expression on tumor cells was assessed using cutoff criteria of ≥1%, ≥5%, and ≥25%. The ORR according to PD-L1 expression level in 48 evaluable TNBC tumors was 6.1% (2 of 33), 7.7% (1 of 13), and 0% (0 of 2), respectively, and this did not appear to impact efficacy. However, an interesting observation was that PD-L1 expression of ≥10% on immune cells within the tumor, so-called "hotspots," was associated with response to avelumab (44% vs 2.6%). Among the 5 TNBC responders, 4 (80%) had the immune-cell "hotspots." Further analysis of PD-L1 expression in the tumor, versus in immune cells within the tumor, as it relates to antitumor activity is warranted.

Notable immune-related and treatment-related AEs included hypothyroidism (grade 1-2, 4.8%), hepatitis (grade 3, 1.8%), and pneumonitis (grade 1-3, 1.8%). These results suggest that in unselected metastatic breast cancer, antitumor activity of a PD-L1 inhibitor is low, but specific subsets, such as TNBC with PD-L1 positivity, experienced clinical benefit. PD-L1 expression in tumor infiltrate in TNBC appeared to be related to clinical response to avelumab.

The A-BRAVE-Trial (NCT02926196) is a phase III randomized trial to evaluate adjuvant treatment with avelumab in 335 patients with TNBC. Patients who complete definitive curative therapy, including surgery, adjuvant chemotherapy (if clinically indicated),

and radiotherapy are eligible if they have more than 4 involved axillary lymph nodes (>pN2) and their adjuvant chemotherapy included at least 3 courses of an anthracycline and 3 courses of a taxane. Patients who undergo neoadjuvant chemotherapy must have pathologic evidence of residual invasive carcinoma in the breast and/or axillary nodes in the definitive surgical specimen. This is a collaborative study between the Istituto Oncologico Veneto IRCCS and the University of Padova and is being conducted in Italy. The primary outcome measure is DFS. The results of this trial will help define the role of an immune-checkpoint–blocking antibody in the adjuvant therapy of TNBC to prevent recurrence.

Durvalumab is an IgG1 monoclonal antibody that binds to PD-L1, thereby blocking its binding to and activation of PD-1 expressed on activated T cells. The FDA has granted accelerated approval to durvalumab for treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy, or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Several studies are testing durvalumab in combination with other agents for early-stage TNBC. This includes a phase Ib study of durvalumab and the PVX-410 vaccine as adjuvant therapy for stage II/III TNBC (NCT02826434); a phase I/II neoadjuvant trial of weekly nab-paclitaxel followed by dose-dense doxorubicin and cyclophosphamide with concurrent durvalumab in stage I-III TNBC (NCT02489448); and a randomized phase II trial of neoadjuvant durvalumab/placebo followed by nab-paclitaxel plus/minus durvalumab followed by epirubicin and cyclophosphamide plus/minus durvalumab (NCT02685059).

For metastatic TNBC, durvalumab is being evaluated in combination with Vigil (autologous tumor cell immunotherapy; NCT02725489), and in combination with paclitaxel (NCT02628132), olaparib (NCT02484404), tremelimumab (NCT02527434), and epacadostat, an inhibitor of indoleamine 2,3-dioxygenase (NCT02318277). Data are not yet available, but forthcoming.

Combination Treatment

Although the sample sizes were small and the patients treated had mostly PD-L1–positive tumors, results from the aforementioned phase I studies are compelling; there were long-lasting clinical responses and a favorable safety profile in a highly pretreated group of metastatic patients with TNBC. In a breast cancer subtype in which response to chemotherapy is typically 4 to 12 weeks, immune-modulating therapy warrants further evaluation, given the observation of durable responses. Several larger-sized trials have been launched with PD-1 and PD-L1 inhibitors based on such encouraging results. However, it seems that the efficacy of single-agent immune checkpoint agents has thus far been limited to a subset of patients who expressed PD-L1. Both monotherapy trials with pembrolizumab and atezolizumab yielded response rates in a pretreated metastatic TNBC population of about 19%. Thus, combination immunotherapy approaches have been evaluated in the hopes of obtaining further improvement in antitumor activity.

Metastatic Setting

Several trials of combination immunotherapy are ongoing. A phase Ib study (NCT01633970) of atezolizumab in combination with nab-paclitaxel in metastatic TNBC was performed.[42] Combining nab-paclitaxel with immunotherapy is attractive, because nab-paclitaxel does not require premedication with steroids, which can cause immunosuppression. PD-L1 expression was assessed on tumor-infiltrating immune cells with the Ventana SP142 antibody, and the expression was scored as IC0, IC1, IC2, or IC3 (if <1%, between ≥1% and <5%, between ≥5% and <10%, or ≥10%, respectively).

In this multi-institution trial, 32 women with TNBC received atezolizumab 800 mg IV on days 1 and 15 with nab-paclitaxel 125 mg/m^2 IV on days 1, 8, and 15 on a 28-day cycle. Median number of previous systemic therapies, including adjuvant and neoadjuvant, was 5 (range, 1-10). Most had prior taxanes (88%). The confirmed ORR in 32 evaluable subjects was 38% (95% CI, 21-56), including 3% CRs and 34% PRs. Stable disease was observed in 44% of patients. In the first-line setting, the confirmed ORR in 13 patients was 46% (95% CI, 19-75). In the second-line setting, the confirmed ORR in 9 patients was 22% (95% CI, 3-60). In the third-line setting and beyond, the ORR in 10 patients was 40% (95% CI, 12-74). At the time of the updated ASCO 2016 presentation, 6 out of 12 responders remained on atezolizumab. ORRs by expression level of PD-L1 were 30% and 36%, respectively, in tumors that were IC0 and IC1, 2, or 3. An interesting observation is that responses were still observed in tumors lacking expression of PD-L1, although responses were slightly higher in tumors defined as PD-L1–positive. Another notable finding was that the responders tended to have higher baseline level of TILs. Though the trial was not powered to show a difference, the response rate was higher in patients who received the combination as first-line therapy compared with the group that had already received prior lines of therapy. Treatment-related grade 3-4 AEs were neutropenia (47%), thrombocytopenia (9%), anemia (6%), and diarrhea (6%).

A large trial effort to evaluate chemoimmunotherapy as first-line treatment in metastatic TNBC was then designed. A phase III randomized (1:1) placebo-controlled trial (IMpassion130; NCT02425891) of atezolizumab in combination with nab-paclitaxel compared with placebo with nab-paclitaxel for patients with previously untreated metastatic TNBC is currently underway.[43] Atezolizumab 840 mg is given IV on days 1 and 15 and nab-paclitaxel 100 mg/m2 is given IV on days 1, 8, and 15 of a 28-day cycle. The co-primary endpoints are PFS and OS. The accrual goal is 900 patients.

A randomized, double-blind, phase III trial (KEYNOTE-355; NCT02819518) is evaluating pembrolizumab and chemotherapy versus placebo and chemotherapy as first-line treatment for metastatic TNBC. Eligible patients must have measurable disease, and those

who have relapsed must have been treated with anthracycline in the adjuvant or neoadjuvant setting unless anthracycline is contraindicated. The study consists of 2 parts. In Part 1, the safety of pembrolizumab in combination with 1 of 3 different cytotoxic regimens will be assessed in patients with metastatic TNBC who have not been previously treated. The chemotherapy agents include nab-paclitaxel, paclitaxel, or gemcitabine/carboplatin. In Part 2, patients with metastatic TNBC who are treatment-naïve will be randomized to treatment with pembrolizumab 200 mg IV on day 1 of each 21-day cycle and chemotherapy or placebo IV (normal saline) and chemotherapy. The chemotherapy can be 1 of the following 3 regimens: 1) nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 of each 28-day cycle, 2) paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 of each 28-day cycle; or 3) gemcitabine/carboplatin 1000 mg/m^2 (gemcitabine) and an area under the curve 2 (carboplatin) on days 1 and 8 of each 21-day cycle. The primary endpoints are OS and PFS in all subjects and in those with PD-L1 positive tumors. The anticipated enrollment is 858 subjects.

Neoadjuvant

Based on the safety experience and potential clinical benefit shown in the metastatic studies, these agents have rapidly been moved for evaluation in the neoadjuvant setting for stage II and III TNBC. Another phase III clinical trial (KEYNOTE-522; NCT03036488) will evaluate the efficacy of pembrolizumab in combination with chemotherapy for neoadjuvant treatment of TNBC. This is a randomized, placebo-controlled trial enrolling women and men presenting with clinical stage IIa (T1cN1) to IIIB TNBC, who are candidates for potentially curative surgery. In this trial, they will first be randomized to pembrolizumab or placebo with weekly paclitaxel and carboplatin (weekly or every 3 weeks) for 4 cycles. This will be followed by treatment for 4 cycles with pembrolizumab or placebo, in combination with doxorubicin (epirubicin can be substituted) and cyclophosphamide, as neoadjuvant therapy prior to surgery. Then, that will be followed by 9 cycles of pembrolizumab or placebo every 3 weeks as adjuvant therapy post surgery. The primary endpoint is pCR, defined as no invasive residual disease in the breast and lymph nodes (ypT0/Tis ypN0). The trial seeks to accrue 855 subjects.

Another phase III neoadjuvant trial (NeoTRIPaPDL1, FM-14-B02; NCT02620280) is evaluating the efficacy of atezolizumab in combination with chemotherapy for TNBC. This is a trial randomizing women with locally advanced triple-negative tumors suitable for neoadjuvant therapy to the combination of nab-paclitaxel and carboplatin with or without atezolizumab. The primary endpoint is event-free survival. The accrual goal is 272 subjects in Europe. The results of these studies will help define the role of an immune checkpoint blocking antibody in the neoadjuvant setting for TNBC.

Conclusion

TNBC is a breast cancer subtype with only chemotherapy as the conventional treatment. Many clinical trials of immunotherapy agents are in progress for the treatment of TNBC. Emerging data in the phase I setting with checkpoint inhibitors demonstrate a tolerable safety profile. Ongoing and future trials will define the role of immune checkpoint blockade in the treatment of TNBC. The hope is that immune checkpoint blocking antibodies will change the standard of care for TNBC.

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Current Treatment Options in Marginal Zone Lymphoma

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Overview
This activity is designed to inform physicians about the current treatment options in marginal zone lymphoma (MZL).

Target Audience
This activity is directed toward medical oncologists, primary care physicians, nurses, and nurse practitioners who treat and/or manage patients with head and neck cancer. Surgical oncologists, radiation oncologists, pathologists, internists, fellows, physician assistants, and other healthcare providers are also invited to participate.

Learning Objectives
After participating in this CME/CE activity, learners should be better prepared to:
- Explain the challenges and unmet needs in MZL, including treatment strategies for patients with relapsed MZL
- Describe the importance of anti-CD20 antibodies in the treatment strategy in MZL
- Discuss the emerging clinical data surrounding the first FDA-approved drug for MZL

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Introduction

Background

Marginal zone lymphoma (MZL) is an indolent, mature, B-cell neoplasm comprising 3 distinct entities: nodal MZL, splenic MZL, and extranodal MZL of mucosa-associated lymphoid tissue (MALT) type.[1] It has been estimated that MZL accounts for approximately 10% to 17% of all newly diagnosed lymphomas.[2-4] Extranodal MZL is the most prevalent, accounting for roughly 7% of all lymphomas, while nodal and splenic MZL each account for <2%.[2] MZL more often affects older individuals, with the median age at diagnosis ranging between 65 and 70 years.[5]

The diagnosis of MZL can be challenging in cases where limited tissue is accessible. Moreover, MZL may be easily confounded for other lymphoma subtypes with similar presentations, morphology, or immunophenotypes. Careful consideration by a multidisciplinary team is often required.[6-8] When splenic MZL is suspected, evaluation of blood and bone marrow morphology, immunohistochemistry, and flow cytometry is usually sufficient, although rare cases may require splenectomy.[9] The diagnosis of nodal and extranodal MZL is dependent on providing the pathologist with relevant clinical information as well as a sufficient quantity and quality of material to perform required testing.

The underlying pathobiology of MZL is chronic immune stimulation, frequently caused by infection or inflammation. For example, *Helicobacter pylori* infection is associated with about 90% of gastric extranodal MZL, the most common extranodal MZL.[10,11] *Chlamydophila psittaci* has been associated with ocular adnexal extranodal MZL,[12] *Campylobacter jejuni* and *Achromobacter xylosoxidans* have been associated with extranodal MZL of the small intestine,[13-15] and hepatitis C virus appears to increase the risk of developing splenic and nodal MZL.[16-19]

Treatment

When MZL is clearly associated with an underlying infectious or inflammatory condition, treatment of that condition may arrest progression of the disease and in some cases, especially *H. pylori*-related gastric MALT lymphoma, can result in complete regression of the tumor.[6,20,21] In cases of asymptomatic MZL that are unlikely to be improved by antimicrobial or other locally directed therapy, a watch-and-wait approach may be appropriate.[22]

Anti-CD20 Antibodies and Chemotherapy

MZL typically has prominent expression of CD20, providing strong rationale for targeting it therapeutically. Rituximab alone or in combination with chemotherapy is reported to provide high response rates in patients with MZL and has been advocated for those with recurrent MZL.[23,24] Several phase II studies have demonstrated that rituximab monotherapy is well tolerated and provides clinical responses when administered as a frontline treatment of MZL.[23,25] The phase III RESORT trial compared maintenance rituximab with a retreatment dosing strategy in asymptomatic patients with indolent lymphomas and low tumor burden. Patients who responded to an initial course of 4 weekly doses of rituximab were randomized to receive an additional dose of maintenance rituximab every 3 months or retreatment with an additional 4 weekly doses at the time of progression. The primary endpoint was time-to-treatment failure (TTF). The reported overall response rate (ORR) was 52.1% in patients with MZL (n = 71). In contrast to follicular lymphoma, where there was no clear advantage to the maintenance strategy, patients with MZL or small lymphocytic lymphoma who received rituximab at each recurrence had a median TTF of 1.4 years compared with 4.8 years in those receiving rituximab maintenance (P = .012). The median time to cytotoxic chemotherapy was 6.3 years in the retreatment arm and was not reached in the maintenance arm, (P = .0002). The overall survival (OS) did not differ between the 2 arms.[26]

Several clinical trials have looked at rituximab in combination with bendamustine or other chemotherapy drugs. In a retrospective study, the efficacy of bendamustine combined with rituximab was examined in the first-line treatment of elderly patients with splenic MZL. A complete response (CR) was reported in 19 of 23 patients (83%) and 3 patients (13%) achieved a partial response. The combination treatment was well tolerated. Toxicities were mild and mainly hematological with 16 of 23 (70%) patients experiencing neutropenia.[27] In a multicenter, phase II trial, rituximab plus cyclophosphamide, vincristine, and prednisone produced an ORR of 88% (95% CI, 77-98) with 24 CRs (60%) among 42 patients with previously untreated MZL.[24] The median duration of response was 28.3 months. After a median follow-up of 38.2 months, the estimated 3-year progression-free survival (PFS) and OS were 59% and 95%, respectively. . Grade 3 or 4 adverse effects (AEs) were neutropenia and febrile neutropenia. In an open-label, randomized, phase III noninferiority trial, rituximab plus bendamustine was compared with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in the first-line treatment of patients with indolent and mantle-cell lymphomas (MCLs), including patients with MZL. Patients with MZL did not show a significant improvement in PFS with rituximab plus bendamustine (HR, 0.70; 95% CI, 0.34-1.43; P = .3249).[28] Interestingly, all other subgroups in this study (follicular lymphoma, MCL, and Waldenström macroglobulinaemia) demonstrated a significant benefit of rituximab plus bendamustine over rituximab plus CHOP.[28] Further studies will be useful in elucidating the efficacy of rituximab in combination with bendamustine or other chemotherapy drugs in patients with MZL.

Other treatment approaches

Historically, splenectomy has been considered a frontline treatment option for patients with symptomatic splenic MZL, although more recently, it seems to be falling out of favor relative to systemic therapies.[29,30] Locally directed surgery or radiation therapy may be a reasonable option for localized disease in selected cases of extranodal MZL.

Ibrutinib

Ibrutinib is the first FDA-approved therapy for MZL and is indicated for the treatment of patients with MZL who require systemic therapy and have received at least 1 prior anti–CD20-based therapy. Ibrutinib is a first-in-class, oral inhibitor of Bruton tyrosine kinase, a key signaling molecule in

the B-cell receptor signaling pathway. In a phase II study in patients with previously treated MZL of all subtypes, 63 patients received ibrutinib 560 mg daily until progression or unacceptable toxicity.[31] In 60 evaluable patients with a median follow-up of 19.4 months, the ORR was 48% (95% CI, 35-62) and the median PFS was 14.2 months (95% CI, 8.3-not estimable). Grade 3/4 AEs that occurred in >5% of patients included anemia, pneumonia, and fatigue. Serious AEs of any grade occurred in 44% of patients.[31]

Pathways to Personalized Medicine

Personalized medicine approaches remain in the investigational stages of development in MZL. There are several oncogenic mutations of genes involved in signaling pathways that have been associated with MZL, including Notch, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), Janus kinase/signal transducer and activator of transcription (JAK/STAT), B-cell receptor, and Toll-like receptor (TLR) signaling.[32-36] In cases of extranodal MZL, the frequency of genetic aberrations is dependent on the primary site of disease.[37] As a greater understanding of the role of signaling pathways in the development of MZL evolves, there will be opportunities for personalizing therapies. It is unclear, however, whether personalized approaches will improve patient outcomes beyond the current treatment paradigm. Clinical trials will be required to determine the roles of signaling pathway inhibition and personalized medicine for patients with MZL.

Peter Martin, MD, MS, associate professor of medicine in the Division of Hematology/Oncology and chief of the Lymphoma Program at Weill Cornell Medicine in New York, offered his insights on current and emerging treatment approaches in patients with MZL.

Moderator: Can you describe some of the unmet needs in the treatment of MZL?

Dr Martin: Fortunately, MZL has some effective therapies available. Principally, rituximab and rituximab plus chemotherapy are active therapies and tend to provide durable responses. That is not to say these treatment options are perfect; there remains room for improvement.

Two areas in MZL where we can do better are the following: First, among patients with mild forms of MZL who might have symptoms or be at risk of developing symptoms, there is a limited number of less-intensive treatment strategies. Rather than give somebody rituximab plus chemotherapy, it would be attractive to use short courses of easily administered agents. For example, someone with localized intestinal MZL may not be particularly symptomatic but is at risk of having worsening symptoms, and it might be attractive to provide occasional therapy to prevent symptoms from emerging. Second, some patients with refractory or relapsed MZL have poor outcomes with current therapeutic approaches and need novel options. For those patients, coming up with therapies that work in ways that are different than chemotherapy might be necessary.

How do treatment strategies differ between MZL subtypes (MALT, nodal MZL, and splenic MZL)?

This question accurately addresses the fact that MZL is a heterogeneous disorder that we classify as nodal MZL, extranodal or MALT lymphomas, and splenic MZL. Even among these lymphomas, there is significant heterogeneity. For example, extranodal MZL might involve the ocular adnexa or the small intestine or the skin or the thyroid gland. The management of a lot of these extranodal lymphomas may depend on the site and extent of disease.

There are a few obvious treatment strategies that make a difference. Certain lymphomas are associated with a clear underlying cause. In general, MZLs arise in the setting of inflammation, and we may be aware of the underlying source of the inflammation. Splenic MZL is frequently associated with hepatitis C; occasionally, nodal MZL can be associated with hepatitis C. Treating the hepatitis C may be sufficient to result in a significant improvement in the lymphoma. Early-stage gastric MZL, in the absence of certain genetic risk factors, has the high probability of responding to *H. pylori* eradication. There are some data that suggest that some ocular adnexal MZL might respond to eradication of *C. psittaci.* There are some circumstances where the management of MZL is dependent on eradication or treatment of the underlying inflammatory condition. Those are probably the minority of all MZLs.

For the remainder of MZLs, the goal of therapy is not only to prevent lymphoma-related symptoms from arising, but also to minimize treatment-related symptoms. The best way to do that often is through observation, and that can be for any MZL subtype. Rituximab and chemotherapy plus rituximab are reasonable options for all subtypes. Some splenic MZLs can be managed surgically, one of the few lymphomas that has surgical management as an option. This is becoming a less attractive option as more effective and better-tolerated systemic therapies become available.

When is a more proactive treatment approach appropriate in an asymptomatic patient? When should the watchful waiting approach be utilized?

All cancers are treated with 3 goals in mind: to cure them when possible, to help patients live longer when possible, and to always to help patients feel better. As long as those are the guiding principles of management of MZL, you cannot really go wrong. Occasionally, localized MZLs can be cured. If patients can be cured in a way that does not induce a lot of toxicity, then that is a reasonable approach. Very often, patients have asymptomatic localized MZL that is in a challenging place to treat, or a systemic MZL, and under these circumstances, the probability of improving somebody's survival by intervening immediately or making them feel better by intervening immediately is very low.

It is important to evaluate whether the lymphoma is likely to cause symptoms in the immediate future. If so, initiating therapy is reasonable. There are official guidelines for clinical trial purposes in follicular lymphoma, called Groupe d'Etude des Lymphomes Folliculaires criteria, which can be applied to MZL, but nothing can replace the combined judgment of a clinician and patient based on repeated interactions and mutual understanding. As we learn more about certain risk factors for lymphomas or risk factors that are involved in the pathogenesis of MZL, that may evolve

over time. For example, if we find that some genetic mutations are likely to be associated with a poor prognosis, that might precipitate earlier therapy. Or, if the lymphoma can be managed by treatment of the underlying condition and not treating the lymphoma, then that is appropriate.

In your opinion, what are some of the promising agents on the horizon that could potentially change the treatment paradigm for MZL?
Increasingly, we are learning more about the biology that drives MZL and the associated heterogeneity. There are clearly roles for multiple signaling pathways, including a B-cell–receptor signaling pathway, a JAK/STAT signaling pathway, TLR signaling, and Notch signaling. There may be a role for antiapoptosis proteins like BCL-2. Provided the interaction between MZL and the microenvironment, immunotherapy might have a role in the future.

Correct identification of active pathways is required through either functional assays or mutational analyses. Clinical trials are required to demonstrate that inhibiting those pathways improves our ability to target the right therapy to the right patient. These are long-term goals in our field. In the short term, the most promising agent on the horizon is probably the agent that was just approved by the FDA for MZL, which is ibrutinib. Ibrutinib provides the opportunity for additional trials in MZL to potentially evaluate which patient population might benefit and evaluate potential combination strategies. Ibrutinib and other B-cell–receptor signaling pathway inhibitors are the most obvious agents to study right now.

The results of the phase II trial, PCYC-1121, were important to the January 2017 FDA approval of ibrutinib in relapsed/refractory MZL. Can you provide us with a brief overview of the findings from this study and the clinical implications?
The study that the FDA approval was based on was called the PCYC-1121 trial. This was an international phase II trial in which 63 patients with previously treated MZL received ibrutinib until time of progression or unacceptable toxicity or withdrawal from therapy for other reasons. These 63 patients had a mix of different kinds of MZL. About half of them had extranodal MZL, and about a quarter each had splenic or nodal MZL. These were typical patients with MZL, with an average age in the mid-60s but ranging from quite young to up to early 90s. Patients had an average of 2 prior therapies. Most commonly, patients had received rituximab plus chemotherapy, and about a quarter of them had received rituximab only. Some patients had received up to 9 prior therapies, so it was a pretty heterogeneous patient population.

In general, the ibrutinib was well tolerated by this patient population. The AEs or toxicity profile were consistent with the toxicity profile seen in other clinical trials in chronic lymphocytic leukemia (CLL), MCL, or follicular lymphoma. Some reported toxicities included gastrointestinal toxicity, myelosuppression with thrombocytopenia, and arthralgias. For the most part, the rates of grade 3 or 4 toxicity were low.

Ibrutinib produced a modest degree of activity in this patient population, with about 50% of patients responding, meaning that about 50% of people had a more than 50% decrease in the diameter of the lymph nodes or extranodal tumors. Among the patients with stable disease, many of them had a mild reduction in the size of their lymph nodes. About 5% to 10% of patients experienced progressive disease as their best response to ibrutinib.

Interestingly, when looking at the population of patients and the potential variables that might influence response or resistance, all different MZL subtypes responded. The extranodal patients responded, as did the splenic and nodal MZL patients; however, the duration of response seemed to be particularly long in the patients with the splenic MZLs compared with the extranodal or nodal MZLs. It is unclear if the duration of response differences were because of underlying disease biology or due to the prior treatment in patients. It did seem as though patients who had fewer prior therapies or rituximab only may have responded a little bit better than the patients who had had chemotherapy in the past. That might be why better responses were seen with the splenic MZL patients who might have been more likely to receive only rituximab in the past.

This is an interesting research question for the future, for sure. Are there differences in these different types of MZLs that might make 1 patient population do better than another patient population? This is something that needs attention in future clinical trials. The average PFS was about 14 months in this study, which is consistent with MCL and not as good as CLL, but a reasonable outcome for a well-tolerated treatment.

Can you discuss promising combination therapies that are being utilized in patients with MZL? How is radioimmunotherapy being utilized?
Radioimmunotherapy is probably something I would be unlikely to include in my treatment regimen for most patients with MZL, unless there is strong rationale for including it. It was included in some of the earlier clinical trials in MZL, and it clearly has activity. However, for whatever reason, clinicians have not widely adopted its use. There are a few scenarios where its use is interesting. For example, in patients with chemotherapy-refractory MZL, it can be an effective option, although radioimmunotherapy may not be as attractive as ibrutinib-based therapy. Radioimmunotherapy demonstrated some activity in ocular adnexal MZL, but the toxicity is not justified by the efficacy in those cases, in my opinion. It is difficult to know where to recommend radioimmunotherapy other than for refractory cases.

Regarding combination therapies, there are not a lot of promising combinations that are currently in the clinic. It is likely we will see combination therapies in the future, in particular with ibrutinib plus rituximab. Considering rituximab is commonly used in MZL treatment, its use in combination with other therapies is a reasonable approach.

What are the toxicity concerns with some of the novel drug agents in the treatment of MZL?
A lot of the newer agents are meant to be used continuously. There are certain toxicities that are associated with chronic use of an agent, where even mild toxicity, drawn out over many months or years, could become a significant nuisance to patients. It is difficult to compare the chronic low-grade toxicity with the more acute and significant toxicity that we run into with immunochemotherapy. Detailed discussions between clinicians

and patients are necessary to determine what each patient values and what their abilities are to tolerate short-term or long-term toxicities of different degrees. There is no question that some of these continuous therapies are going to have some toxicities. In general, these agents are better tolerated than chemotherapy, but are also given over longer periods of time. One of the toxicities that we will all have to struggle with as a population is financial toxicity—that is associated with some of these newer drugs.

How may B-cell receptors, JAK/STAT, NF-κB, Notch, and TLR signaling pathways help evolve personalized treatment approaches?

MZL is a great target for personalized medicine approaches, but it's still in the investigational stages. Currently, there is 1 drug that's approved for MZL, which is ibrutinib. There are no other approved drugs in MZL for all the other noted pathways (eg, JAK/STAT signaling pathway, TLR signaling, and Notch signaling). If we could sequence every single MZL, it is not clear we would necessarily be able to offer the therapies that the sequencing data might suggest we should. Additionally, it remains to be seen whether the personalized medicine approach improves patient outcomes beyond the outcomes already seen with our current approaches. For example, patient outcomes may be decent with observation and single-agent rituximab, regardless of whether a TLR signaling pathway is overactive.

There is room for improvement in MZL disease treatment, and personalized medicine is an attractive approach, as we understand there is a role of these signaling pathways. However, it may be too early to say what role precision medicine will have in the future, and it is too early to start using precision medicine as a standard to manage most patients with MZL.

What is the role of monoclonal antibodies, specifically anti-CD20 antibodies, in the treatment paradigm for MZL?

The anti-CD20 antibodies are some of the most important drugs in the management of most MZLs. They can improve the response to chemotherapy. For example, improvement in response has been demonstrated in extranodal MZL through a phase II trial combining rituximab plus chlorambucil compared with chlorambucil alone.[38] Several clinical trials have looked at rituximab in combination with bendamustine or other chemotherapy drugs, and rituximab is well tolerated and active.[27] Anti-CD20 antibodies clearly have a role whenever chemotherapy is utilized.

In addition, anti-CD20 monoclonal antibodies have significant single-agent activity, and where this has potentially been best studied is splenic MZL. Historically, splenectomy was considered frontline therapy for splenic MZL. Now it is clear that similar results can be achieved using a short course of rituximab alone. Rituximab can sometimes be associated with more AEs than might otherwise be experienced with other indolent lymphomas.

Anti-CD20 antibodies clearly have significant single-agent activity in splenic MZL, and a lot of clinicians are using them in patients with extranodal MZLs or localized extranodal MZLs where chemotherapy or radiation therapy is not appropriate. There is no question that these anti-CD20 antibodies are the mainstay for most patients with MZL and will remain so for the foreseeable future. Unfortunately, these agents do not offer a cure to patients with MZL and can lead to relapse. There is a need to examine new drugs that can work in combination with anti-CD20 antibodies.

What are the challenges when managing the treatment of a patient with relapsed or refractory MZL?

Clinicians need to remember that when managing relapsed MZL, relapse of MZL is not the same as a relapse of diffuse large B-cell lymphoma. If the lymphoma has come back or started to grow, it does not mean that the patient necessarily needs treatment immediately. It is often that patients with progressive MZL can be observed, just as they were observed when originally diagnosed with lymphoma. Clinicians need to be careful not to overtreat people with MZL. On the other hand, there are some patients with MZL who have either a more aggressive variant of MZL, a more chemotherapy-refractory MZL, or can experience transformation to an aggressive histology. Although these patients are the minority, they can be very challenging to manage, and this is where there is clearly an unmet need and new strategies need to be developed.

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