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From the Editor

In the January 2015 issue, we cover new territory with topics not presented in previous issues. Cervical cancer remains a significant cause of cancer worldwide, even with highly successful screening. While it is hoped that wider screening, which has now been adapted to detect oncogenic papilloma viruses, along with papilloma virus vaccination, will reduce the incidence of this disease, our only effective treatments for early-stage disease are surgical or ablative. For many years, concurrent radiation and platinum chemotherapy remained the only effective therapy for higher-stage and nonmetastatic disease.

While advanced recurrent cervical cancer remains incurable, a review on this topic by Drs Steven Yu and Agustin Garcia highlight newer therapies that include bevacizumab added to chemotherapy, which received FDA approval last year. Immunotherapy is showing early promise, possibly due to the immunogenicity of a virally driven cancer, and larger scale trials are now under way.

Another feature review covers the difficult-to-manage syndrome of chemotherapy-induced peripheral neuropathy (CIPN), which is poorly understood physiologically and is clinically manifested in variable fashion in terms of onset and chronicity. Drs Trivedi, Hershman, and Crew provide a very helpful overview on the physiology and clinical spectrum of CIPN, with strategies on surveillance and grading—an approach that should become standard practice. The difficulty in managing CIPN is highlighted, with a review of approaches with demonstrated benefit, but an acknowledgment that responses are variable and far from adequate, highlighting the need for more research and awareness of this common treatment side effect.

A review on EGFR-targeting therapy for lung cancer from Drs Ogunleye, Ibrahim, Stender, Kalemkerian, and Jaiyesimi highlights how far we have come in genomic medicine in both understanding the molecular biology of cancer as well as harnessing drug development capabilities to develop small molecules targeting genomic lesions. Lung cancer rapidly transformed from a disease uniformly treated with upfront chemotherapy to one now approached with careful molecular characterization and customized therapy. The nature of drug-sensitizing and resistance-associated *EGFR* mutations is described along with the rationale for specific therapies and optimal sequences—all of which are still evolving in this rapidly changing field.

The much more established area of adjuvant therapy for HER2+ breast cancer is covered with a focus on the controversial topic of small node-negative (T1a/bN0) tumors, where the minor benefits must be traded off against side effects and cost. The lack of randomized trials, which would not be feasible to perform because of the large sizes needed, has led to the testing of a less-toxic trastuzumab-containing regimen using a single-arm trial that constitutes one of several options for this not-so-uncommon scenario, as described in a review authored by Dr Yap and myself.

The CME article in this issue uses a roundtable discussion format to navigate the intricacies of immunotherapy and signal transduction-targeting treatment for advanced melanoma. The nuances of real-life oncology practice that include choosing the best sequence for patients with *BRAF*-mutated melanoma, or how to manage brain metastases, are effectively covered. This format is ideal for airing expert opinions on how to assess and manage toxicities with dual BRAF and MEK inhibitor therapy, an area that requires experience and skill—a high priority for a CME activity.

Finally, it is a pleasure to introduce our newly appointed *AJHO* Associate Editor, Myron Czuczman, MD, from the Roswell Park Cancer Institute, who provides a review of key lymphoma abstracts from the 2104 American Society of Hematology (ASH) annual meeting.

Debu Tripathy, MD
Editor-in-Chief

Management of Chemotherapy-Induced Peripheral Neuropathy

Meghna S. Trivedi, MD, Dawn L. Hershman, MD, MS, Katherine D. Crew, MD, MS

Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is a common adverse effect of several commonly used cancer treatments, including taxanes, platinum agents, and vinca alkaloids. Sensory symptoms in the hands and/or feet, typically in a "stocking-glove" pattern, are common, and manifested as pain, numbness, and/or tingling. CIPN can result in chemotherapy dose reduction or discontinuation, and can also have long-term effects on quality of life. The course of CIPN can be unpredictable: while symptoms may resolve after chemotherapy is discontinued, they can also continue for years. There are several methods available to assess CIPN: objective measures include physical examination and neurophysiological testing and subjective measures include the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading scale and patient-reported outcome measures. While many interventions have been studied for CIPN prevention and treatment, only duloxetine has proven efficacy for treatment. Given the clinical implications of CIPN, there is great interest in better understanding its pathophysiology, standardizing evaluation, and developing effective treatments.

Key words: Chemotherapy-induced peripheral neuropathy, prevention, treatment, outcomes measures.

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common adverse effect of many anticancer drugs, such as platinum analogs, antitubulins (eg, taxanes and vinca alkaloids), bortezomib, and thalidomide.[1] It can present as sensory symptoms in the hands and/or feet, typically in a "stocking-glove" pattern; pain, numbness, or tingling; or motor symptoms, manifested as weakness, cranial nerve deficits, or autonomic neuropathy.[2] In a recent meta-analysis of 31 CIPN studies involving 4179 patients, the aggregate prevalence of CIPN was 48%.[3] Within the first month of completing chemotherapy, the prevalence of CIPN was 68.1%; after 6 or more months of completing chemotherapy, the prevalence of CIPN decreased to 30.0%.[3] The course of CIPN can be unpredictable, and although some symptoms may improve with time, others may persist or worsen as a result of permanent nerve damage.[1] There are limited data on the natural history of CIPN in long-term cancer survivors, who are beyond 1 year of completing chemotherapy. Patients with breast cancer, who received taxane-based adjuvant chemotherapy, had neuropathy symptoms up to 2 years after completing treatment,[4] and patients with colon cancer receiving oxaliplatin-based adjuvant chemotherapy had numbness or tingling of hands and feet up to 6 years from starting treatment.[5]

One of the challenges in managing and preventing CIPN is that the exact pathophysiology is not well understood. The hypothesized mechanisms of taxane-induced neuropathy include the disruption of the axonal microtubule structure and a deficit in axonal energy supply from the toxic effect of chemotherapy on mitochondria in primary afferent neurons.[2,6] CIPN due to vinca alkaloid therapy is thought to be due to alterations in the neuronal cytoskeleton that cause axonal degeneration.[2,6] Platinum agents are thought to cause CIPN by exerting damage in the dorsal root ganglion through mitochondrial dysfunction and neuronal apoptosis, either by DNA crosslinking or oxidative stress.[2,6]

Despite investigations leading to hypotheses of several mechanisms of CIPN, none has resulted in clinically relevant therapeutic interventions.[7] Several studies have attempted to identify risk factors for CIPN development, which also vary with different chemotherapeutic agents. Some of the clinical factors implicated in the development of CIPN include baseline neuropathy,[8,9] the presence of diabetes,[9] smoking history,[10] and decreased creatinine clearance.[10] In addition, there is interest in pharmacogenomics and identifying genes that may play a role in the development of CIPN. Although numerous genes have been investigated, such as *GSTP1, CYP2C8,* and *AGXT*, there have been no conclusive findings.[11]

One of the clinical implications of CIPN is that the symptoms can result in treatment dose reduction or discontinuation, which may ultimately affect overall survival.[2] In a retrospective single-institution study of 123 patients with breast cancer receiving tax-

ane-based adjuvant or neoadjuvant chemotherapy regimens, 17% received chemotherapy dose reductions specifically due to CIPN that developed during treatment.[12] In addition, for cancer survivors, CIPN symptoms can significantly impact quality of life.[1,7,13]

This review article will discuss the methods used to assess CIPN and review the trials investigating its management. The American Society of Clinical Oncology (ASCO) recently published a systematic review of 48 randomized controlled trials providing guidelines on prevention of and treatment approaches to CIPN,[14] which will be summarized here.

Practical Application

- CIPN is a common adverse effect of several chemotherapy agents that can affect patient quality of life and adherence to cancer treatment.
- Although there are many methods to assess and grade CIPN, a standardized method has not been established.
- Duloxetine is the only intervention with efficacy for the treatment of CIPN demonstrated from a randomized, double-blind, placebo-controlled trial.

Assessment of CIPN

There are several methods available to assess CIPN; however, there is no consensus on *the* best method. There are objective assessments, such as clinical or neurophysiological examinations, and subjective assessments, such as the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading scale and patient-reported outcome measures. Other causes of neuropathy (ie, diabetic neuropathy) should also be entertained in a patient with symptoms.

The objective assessments can be either invasive or noninvasive. Noninvasive methods to assess CIPN include neurological assessment on physical examination to identify sensory and motor deficits and vibration sensation measurement.[1] Nerve conduction studies are an invasive method and will typically reveal a reduction in the amplitude of the sensory nerve action potentials (SNAPs).[2] However, this procedure can cause discomfort to the patient without providing additional clinical information.[1] In addition, nerve conduction studies detect abnormalities in large-diameter nerve fibers, not the small-size fibers that are involved in painful CIPN.[1]

NCI-CTCAE Version 4.03 is a subjective method to evaluate CIPN: it is performed by a healthcare professional, who grades adverse events that include peripheral sensory or motor neuropathy, dysesthesia, paresthesia, and neuralgia on a scale of 1 to 5, depending on the severity.[15] The advantage of the NCI-CTCAE is that the assessment is quick and easy for providers to perform.[16] However, it is limited by the subjectivity of interpretation; lack of detail about location, type, and severity of impairment; and a narrow scoring range.[1]

There are several patient-reported outcome measures that can be used to assess CIPN, and there is evidence that these measures are more accurate and sensitive at reporting patients' symptoms compared with such physician-reported measures as the NCI-CTCAE.[4,17] Postma et al[18] developed a CIPN subscale as part of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire 30 (QLQ-30), the QLQ-CIPN20 module. The instrument contains 20 questions evaluating sensory, motor, and autonomic symptoms, and has been validated as an assessment tool for CIPN.[19] Another patient survey used to assess CIPN is the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) questionnaire.[20] This validated and reliable tool uses 11 questions to evaluate the severity of neuropathy and its impact on patient quality of life.

Composite scales that combine invasive and noninvasive objective measures, as well as subjective measures, are also available, with the most frequently used scale being the Total Neuropathy Score (TNS).[1,21] The TNS includes subjective provider-scored sensory, motor, and autonomic symptom measures; noninvasive objective measures of pin sensibility, vibration sensibility, strength, tendon reflexes, and quantitative sensory testing; and invasive objective measures of sural and peroneal nerve conduction studies.[21] In a single-institution study of 60 women with CIPN secondary to cisplatin and paclitaxel, the TNS results correlated well with those obtained from the NCI-CTCAE scales.[21] The disadvantages of the TNS are that it is time-consuming to administer, requiring approximately 1 hour, and requires specialized instrumentation.[16,21] There is a version of the TNS that does not use quantitative sensory testing, known as the TNS-reduced (TNSr) scale, and a version that uses only the clinical evaluation of symptoms and signs, known as TNS-clinical (TNSc) scale.[16] A study by Cavaletti et al[22] demonstrated that the TNS and TNSc are more sensitive than the NCI-CTCAE and provide more accurate grading of CIPN. The challenge is how to incorporate these CIPN measures into clinical practice and standardize this approach across multiple centers.

Prevention of CIPN

The recently published ASCO guidelines on the prevention of CIPN, based on a systematic review of 42 randomized controlled trials investigating 18 agents, found that there are no agents that have shown consistent, clinically meaningful benefits for CIPN prevention.[14] Investigations of intravenous calcium/magnesium for oxaliplatin-induced neuropathy[23] and oral vitamin E[24] have shown no benefit in prevention of CIPN. Two agents have actually been shown to worsen CIPN compared with placebo: acetyl-L-carnitine (ALC) and nimodipine.[25,26] ALC is a natural compound that has been shown to improve sensory neuropathy and reduce the severity of neuropathy development in a rat model.[27] In a single-arm study by Bianchi et al[28] of 25 patients with established CIPN due to paclitaxel or cisplatin, there was improvement in sensory and motor neuropathy with 3-times-dai-

TABLE. Phase 3 Randomized, Placebo-Controlled CIPN Treatment Trials

Drug Class	Pharmacologic Agent and Dosage	Authors and Year of Publication	Number of Patients and Study Design	Drug Causing CIPN	Primary Study Outcome Measure and Results	Overall Results	Adverse Effects of Intervention
Antidepressant	Amitriptyline 10 mg daily with dose escalation of 10 mg/week up to target maximum dosage of 50 mg daily for 8 weeks	Kautio et al, 2008[39]	Total: 33 Placebo: 16 Amitriptyline: 17 Double-blind study	Vinca alkaloids, platinum agents, or taxanes	• Global improvement as assessed by numeric scales (scale, 0-10) in diary data: no significant difference in mean score between groups (3.4±3.6 vs 1.9±3.1 in placebo arm; *P* = NS). • Global improvement at final visit assessed by verbal rating scale (scale, complete relief-symptoms worse): no significant difference between groups (47% vs 31% in placebo arm; *P* = NS).	Negative	Tiredness Tachycardia
	Nortriptyline (N) 25 mg daily with dose escalation of 25 mg/week up to target maximum dosage of 100 mg during treatment period	Hammack et al, 2002[38]	Total: 51 Group A (N/PL): 26 Group B (PL/N): 25 Double-blind crossover study after 4 weeks	Cisplatin	• Paresthesia as assessed by visual analog scale: in first treatment period, no significant reduction in paresthesia (49 vs 55 [scale, 0-100] in placebo arm; *P* = .78).	Negative	Dry mouth Dizziness Constipation
	Venlafaxine 50 mg 1 h prior to oxaliplatin infusion and 37.5 mg extended-release twice daily on days 2 through 11	Durand et al, 2012[40]	Total: 48 Placebo: 24 Venlafaxine: 24 Double-blind study	Oxaliplatin	• Full relief of acute neurotoxicity: 31.3% vs 5.3% in placebo arm (*P* = .03).	Positive	Grade 1-2: nausea and vomiting, asthenia, somnolence
	Duloxetine (D) 30 mg daily for 1 week, then 60 mg daily for 4 weeks during treatment period	Smith et al, 2013[46]	Total: 220 Group A (D/PL): 109 Group B (PL/D): 111 Double-blind crossover study after 5 weeks	Paclitaxel, docetaxel, nanoparticle albumin-bound paclitaxel, cisplatin, oxaliplatin	• Reduction in average pain as measured by BPI-SF: in initial treatment period, larger mean reduction in BPI-SF pain score in duloxetine group than placebo group (1.06 vs 0.34 [scale, 0-10]; *P* = .003) with moderately large effect size (0.513).	Positive	Fatigue (7%) Insomnia (5%) Nausea (5%)

ly dosing of 1 g of ALC for 8 weeks with little toxicity. However, when studied in a large randomized, double-blind, placebo-controlled trial of 409 patients with breast cancer initiating adjuvant taxane-based chemotherapy, ALC was found to significantly increase CIPN.[25] Also, nimodipine was found to have a neuroprotective effect against cisplatin in a rat model,[29] and when studied in a small randomized, placebo-controlled trial of 51 patients, it exacerbated neurotoxicity in patients receiving cisplatin for treatment of ovarian cancer.[26]

Glutathione is a natural compound composed of the 3 amino

TABLE. Phase 3 Randomized, Placebo-Controlled CIPN Treatment Trials *(continued)*

Drug Class	Pharmacologic Agent and Dosage	Authors and Year of Publication	Number of Patients and Study Design	Drug Causing CIPN	Primary Study Outcome Measure and Results	Overall Results	Adverse Effects of Intervention
Antiepileptic	Gabapentin (G) 300 mg with dose escalation of 300 mg to a target maximum dosage of 2700 mg daily for 6 weeks during treatment period	Rao et al, 2007[36]	Total: 115 Group A (G/PL): 57 Group B (PL/G): 58 Double-blind crossover study after 6 weeks	Vinca alkaloids, taxanes, or platinum agents	• "Average" pain by NRS and ENS: no difference in NRS or ENS score at baseline, 6 weeks, or 14 weeks between groups.	Negative	No significant differences in toxicities between groups
	Lamotrigine 25 mg at bedtime for 2 weeks, then 25 mg twice daily for 2 weeks, then 50 mg twice daily for 2 weeks, then 100 mg twice daily for 2 weeks, then 150 mg twice daily for 2 weeks	Rao et al, 2008[37]	Total: 125 Placebo: 62 Lamotrigine: 63 Double-blind study	Vinca alkaloids, taxanes, or platinum agents	• "Average" pain by NRS and ENS: no difference in NRS or ENS score at baseline or 10 weeks between groups.	Negative	No significant differences in toxicities between groups
Topical	Baclofen, amitriptyline, and ketamine gel, 1.31 g of compounded gel containing 10 mg baclofen, 40 mg amitriptyline HCL, and 20 mg ketamine twice daily for 4 weeks	Barton et al, 2011[41]	Total: 203 Placebo: 102 BAK gel: 101 Double-blind study	Vinca alkaloids, platinum agents, taxanes, or thalidomide	• EORTC CIPN sensory subscale mean neuropathy change from baseline to 4 weeks: 8.1 vs 3.8 in placebo arm (P = .053).	Negative	No significant differences in toxicities between groups
	Amitriptyline and ketamine (AK) cream 4 g twice daily for 6 weeks	Gewandter et al, 2014[42]	Total: 458 Placebo: 231 AK: 227	Taxanes or nontaxanes	• Mean pain, numbness, and tingling score at week 6: no significant reduction in mean score (P = .363)	Negative	No significant differences in toxicities between groups

BPI-SF indicates Brief Pain Index-Short Form; CIPN, chemotherapy-induced peripheral neuropathy; EORTC, European Organisation for Research and Treatment of Cancer; ENS, ECOG Neuropathy Scale; NRS, Numerical Rating Scale.

acids glutamic acid, cysteine, and glycine that has been extensively studied for CIPN prevention—but with mixed results.[30] In mouse studies, when glutathione was given with cisplatin, the platinum concentration in the dorsal root ganglia was lower and sensory nerve conduction velocity decreased less compared with mice that received only cisplatin.[31] And there have been several small placebo-controlled trials which have shown that intravenous administration of glutathione with platinum-based chemotherapy regimens can decrease the incidence of neurotoxicity without diminishing the effect of chemotherapy.[32-35] Leal et al[30] studied the use of glutathione with carboplatin and paclitaxel and found no improvement in neurotoxicity symptoms, suggesting that glutathione may not help in taxane-induced CIPN.

Treatment of CIPN

Eight agents have been studied in randomized controlled trials for the treatment of CIPN, but there has been limited success. The characteristics and results of these studies are summarized in the **Table**. Clinical trials of the antiepileptic agents gabapentin[36] and lamotrigine[37] and the antidepressants nortriptyline[38] and amitriptyline[39] have all been negative.

In the EFFOX study,[40] Durand et al investigated the EFFicacy of venlafaxine for prevention and relief of OXaliplatin-induced acute neurotoxicity. In this small placebo-controlled trial of 48 patients, venlafaxine was shown to provide relief of recurrent acute neurotoxicity and decrease the incidence of cumulative permanent neurosensory toxicity following completion of oxaliplatin treatment. The mechanism of efficacy for venlafaxine was

thought to be through a protective effect against oxaliplatin-induced oxidative stress.[40]

A topical mixture of baclofen, amitriptyline, and ketamine (BAK) was developed by Barton et al[41] to treat CIPN in a group of patients who had numbness, tingling, or pain associated with peripheral neuropathy while receiving or after having received neurotoxic chemotherapy. The investigators hypothesized that since there may be several complex pathways resulting in CIPN, a combination of drugs with unique but complementary mechanisms of action may be beneficial in treatment. The patients applied the topical treatment twice daily for 4 weeks. Compared with placebo, the topical treatment resulted in an improvement in motor neuropathy and a trend toward improvement in sensory neuropathy; however, the overall effect was modest.[41] Gewandter[42] studied the use of topical amitriptyline and ketamine twice daily for 6 weeks and found no significant reduction in the pain, numbness, or tingling score at the end of topical treatment.

Duloxetine is a neuronal serotonin and norepinephrine reuptake inhibitor that has been shown to be effective in the treatment of diabetic neuropathy.[43-45] A phase 3, randomized, double-blind, placebo-controlled crossover trial evaluated the use of duloxetine in the treatment of painful CIPN.[46] Forty percent of patients in this study received paclitaxel, and 59% of patients received oxaliplatin as the neurotoxic agent. The study used the Brief Pain Inventory-Short Form (BPI-SF) as the primary outcome measure in patients with established CIPN, and found that duloxetine use resulted in a greater mean reduction in pain (scale, 0-10) of 1.06 compared with 0.34 in the placebo arm (effect size, 0.513; $P = .003$).[46] Based on the results of this study, the ASCO clinical practice guidelines give a moderate recommendation for the use of duloxetine in patients with cancer experiencing CIPN.[22]

Future Directions in Treatment of CIPN

Clinical trials investigating complementary and alternative medicine in the treatment of CIPN, such as acupuncture (NCT02129686) and massage therapy (NCT02221700), are under way. A few small trials have investigated the use of Scrambler therapy, a device that provides noninvasive cutaneous electrostimulation, to treat CIPN and found efficacy with no toxicity.[47-49] A randomized, double-blind trial to evaluate Scrambler therapy is under way (NCT02111174) now. The use of topical menthol for CIPN is also being investigated in a placebo-controlled, randomized trial (NCT01855607) after the encouraging results of a phase 1 study showing improvement in CIPN pain and function with a 6-week course of twice-daily application of 1% topical menthol to affected areas.[50]

Conclusions

CIPN is a frequent complication of cancer treatment that can not only affect a patient's response to treatment, due to the need for dose reduction or discontinuation, but also quality of life. Although treatment and prevention options for CIPN are limited at present, the use of duloxetine for painful CIPN can be recommended based on the results of a positive phase 3 trial. It is also reasonable to try tricyclic antidepressants, gabapentin, or topical BAK after discussing the limited evidence, risks, and benefits with the patient. However, patients undergoing treatment with causative agents should undergo assessment by their treating physician for CIPN symptoms, using NCI-CTCAE criteria and clinical examination, and perhaps validated patient-reported outcome measures. Understanding the pathophysiology of CIPN and the ability to accurately and consistently assess CIPN are 2 major challenges in the treatment of CIPN. There is great interest in not only the investigation of interventions to treat CIPN, but also in investigations to better understand and characterize this treatment-related adverse effect.

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A Review of the Management of T1a/bN0 HER2-Overexpressed Breast Cancer

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Abstract

Small node–negative breast cancers measuring less than 1 cm (pT1a/bN0) are generally associated with a favorable prognosis. However, as many as 10% of these breast cancers exhibit human epidermal growth factor receptor 2 overexpression and/or amplification (HER2+). Chemotherapy + trastuzumab is the accepted adjuvant therapy for early HER2+ breast cancers as it lowers the risk of recurrence and mortality, but virtually all patients enrolled in the pivotal trials for this therapy had a higher stage of disease. Several large retrospective reviews have reported a lower overall survival among HER2+ cases in the pT1a/bN0 patient group. The use of chemotherapy with trastuzumab has increased significantly despite the lack of direct evidence for the efficacy of trastuzumab in pT1a/bN0 breast cancers. This review addresses the current data regarding the prognosis of pT1a/bN0 breast cancers and outcomes of patients receiving HER2-targeted therapy.

Key words: HER2, node negative, T1a, T1b, trastuzumab, breast cancer.

Introduction

Human epidermal growth factor receptor 2 overexpression (HER2+), an oncogenic receptor and poor prognostic factor, is found in 15% to 20% of all breast cancers. Although less frequent, HER2+ is found in as many as 10% of node–negative breast cancers less than 1 cm (ie, pT1a/bN0).[1-3] HER2-targeted therapy with trastuzumab and chemotherapy has significantly lowered recurrence and mortality risk in the treatment of early-stage HER2+ breast cancers, but very few patients with pT1a/bN0 tumors were enrolled in the key trials. Therefore, the management of small node–negative HER2+ breast cancer remains unclear as small node–negative breast cancers are generally associated with a favorable prognosis and trastuzumab-based treatment can result in both short- and long-term complications. Despite the lack of robust evidence, there had been a significant increase in the use of chemotherapy with trastuzumab in these patients over the last decade.[4] In this article, we will review the literature of pT1a/bN0 HER2+ breast tumors and the efficacy of trastuzumab in these patients.

Natural History of pT1a/bN0 HER2-Overexpressed Breast Tumors

HER2 overexpression has both prognostic and predictive value. Patients with HER2+ tumors have a higher risk of recurrence. Small node–negative breast cancer, especially those <1 cm, generally carries a favorable prognosis. One of the first studies to suggest HER2+ as a risk factor for recurrence in this subset was a Finnish study published in 2003.[5] In this retrospective review of 852 patients with stage I breast cancer, 313 patients had pT1a/bN0M0 tumors. HER2 status was documented in 194 patients. Among these patients, those with moderately or poorly differentiated breast tumors had lower distant disease-free survival (DDFS) only if their tumors were HER2+ (9-year survival, 92% vs 67%; $P = .003$).

This finding was further reinforced by 2 large retrospective reviews. In the MD Anderson series that consisted of 965 patients with pT1a/bN0 breast tumors not treated with adjuvant chemotherapy or trastuzumab, patients with HER2+ tumors had a higher risk of recurrence (hazard ratio [HR], 2.68; 95% CI, 1.44-5.0; $P = .002$) and distant recurrence (HR, 5.3; 95% CI, 2.23-12.62; $P < .001$) than those with HER2– tumors.[3] The 5-year recurrence-free survival (RFS) was 77.1% and 93.7%, respectively, for HER2+ and HER2– breast cancers. The European Institute of Oncology group identified 2130 patients with pT1a/bN0 breast tumors; 150 had HER2+ breast tumors. None of these patients received adjuvant trastuzumab. They reported a lower 5-year DFS in patients with pT1a/bN0 HER2+ breast cancers (HR, 2.4; 95% CI, 0.9-6.5; $P = .09$).[1] In this series, HER2+ status was associated with a worse prognosis in hormone receptor–positive breast cancer compared with their hormone receptor–negative counterparts (HR, 5.1; 95% CI, 1.0-25.7).

A National Comprehensive Cancer Center Network (NCCN) database review recently reported a 5-year overall survival exceeding 95% in patients with pT1a/bN0 breast tumors who were not treated with chemotherapy or trastuzumab. For patients with untreated pT1aN0 HER2+ breast tumors, the 5-year overall survival was 95% (95% CI, 88-98; n = 102) in hormone receptor–positive and 93% (95% CI, 79-98; n = 49) in hormone receptor–negative patients, respectively. The 5-year overall survival in patients with untreated pT1bN0 HER2+ breast cancers was 95% (95% CI, 88-98; n = 89) and 100% (n = 17) in hormone receptor–positive and hormone receptor–negative patients, respectively.[4] The overall survival did not appear to be significantly different between

TABLE 1. pT1a/bN0M0 HER2+ Breast Cancer Outcomes

Study	Study Type	No. of Patients	Findings
Finnish 2003[5]	Retrospective review	194 (<5% received adjuvant therapy) (23 HER2+)	9-year DDFS 92% vs 67% in moderately and poorly differentiated HER2 unamplified (n = 56) and amplied (n = 12) tumors, respectively
MD Anderson 2009[3]	Retrospective review	965 untreated patients (98 HER2+)	5-year RFS 77.1% vs 93.7% Distant recurrence HR 5.3 (95% CI, 2.23-12.62; *P*< .001)
EIO 2009[1]	Retrospective review	2130 untreated patients (150 HER2+)	5-year DFS HR 2.4 (95% CI, 0.9-6.5; *P* = .09) HR+ vs HR: HR 5.1 (95% CI, 1-25.7)
NCCN 2014[4]	Retrospective review	3401 untreated patients (257 HER2+)	5-year OS, pT1aN0 HR+ 95% (95% CI, 88-98; n = 102) HR– 93% (95% CI, 79-98; n = 49) 5-year OS, pT1bN0 HR+ 95% (95% CI, 88-98; n = 89) HR– 100% (n = 17)
KPNC 2014[6]	Retrospective review	234 HER2+ (171 untreated)	5-year DRFI T1a 99% (95% CI, 93-99.9%) T1b <1.0 cm 100% T1b 1.0 cm 93.3% (95% CI, 75.9-98.3%) HR+ 98.1% (95% CI, 92.6-99.5%) HR = 98.4% (95% CI, 88.9-99.8%)

DDFS indicates distant disease-free survival; DFS, disease-free survival; DRFI, distant recurrence-free interval; HR, hazard ratio; HR-, hormone receptor-negative; HR+, hormone receptor-positive; OS, overall survival; RFS, recurrence-free survival.

the hormone receptor–positive and hormone receptor–negative groups. However, no direct comparison was made between these groups.

The Kaiser Permanente Northern California (KPNC) tumor registry also identified 171 patients with untreated HER2+ pT1a/bN0 breast tumors. A lower 5-year distant recurrence–free interval (DRFI) was reported in patients with T1bN0 HER2+ tumors measuring 1 cm compared with smaller tumors.[6] The 5-year DRFI was 99% (95% CI, 93-99.9%), 100%, and 93.3% (95% CI, 75.9-98.3%) for T1a, T1b measuring less than 1 cm, and T1b measuring 1 cm, respectively. Similar to the NCCN database review, the 5-year DFRI did not appear to be different between the hormone receptor–positive and hormone receptor–negative patients (98.1% vs 98.4%). In summary, retrospective outcomes series of pT1a/bN0 HER2+ breast tumors show wide ranges in outcomes, with some, though not all, suggesting a higher recurrence risk in HER2+ compared with HER2– cases—overall, still an excellent outcome. It is important to determine baseline recurrence risk, as the benefit of systemic adjuvant therapy is generally proportional to the risk.

Benefits of HER2-Targeted Therapy

Several large randomized multicenter studies have shown that the addition of trastuzumab to chemotherapy results in decreased recurrence and better OS. This knowledge has led to new standards for, and widespread use of, trastuzumab-based therapy for early-stage HER2+ breast cancer.[7-9] However, none of the 4 pivotal studies included patients with pT1a/bN0 breast cancers, with the exception of the BCIRG-006 trial, which included T1a/b breast tumors. Although not specifically mentioned, these tumors were likely node-positive. Nevertheless, at present, there is lack of data from controlled studies regarding the efficacy or magnitude of benefit of adjuvant trastuzumab for pT1a/bN0 breast cancers.

In a French multicenter retrospective review of 276 cases of pT1a/bN0 HER+ breast tumors, 129 patients (47%) were treated with adjuvant trastuzumab-based chemotherapy (ATBC+), 19 with chemotherapy alone, 5 with trastuzumab alone, and 123 (45%) with neither trastuzumab nor chemotherapy (ATBC–).[10] The receipt of ATBC was significantly associated with hormone receptor–negative status, high Ellston-Ellis (EE) grade, tumor

TABLE 2. Benefits of HER2-Targeted Therapy in pT1a/bN0 Breast Cancer

Study	Study Type	No. of Patients	Findings	Remarks
French[10]	Retrospective	276 (129 ATBC+, 123 ATBC-)	90-month DFS 99% in ATBC+ and 93% in ATBC- cases (*P* = .018)	Decision to use ATBC was associated with hormone receptor–negative status, high Ellston-Ellis (EE) grade, tumor size, and patient age
APT trial[11]	Prospective phase 2 for T≤3 cm, node-negative HER2+ tumors	201 pT1a/bN0 cases	3-year DFS 99.5% (95% CI, 98.4%->99.9%	For all patients, 3-year DFS 98.7% (95% CI, 97.6-99.8%)

ATBC indicates adjuvant trastuzumab-based chemotherapy; DFS, disease-free survival.

size, and patient age. Despite this selection bias, there were only 2 recurrences in the ATBC+ group but 13 in the ATBC– group at a median follow-up of 44 months, with a 40-month DFS of 99% and 93%, respectively (*P* = .018).

A prospective randomized trial of trastuzumab-based treatment would ideally support the potential benefit of this approach in patients with pT1a/bN0 HER2+ breast cancers. Until recently, no such studies had been conducted due to several limitations, such as low incidence, which could limit recruitment of participants; ethical concerns about involving a no-treatment placebo group; and concerns about potential long-term toxicities in women with a good prognosis. In view of these challenges, Dana-Farber Cancer Institute designed a phase 2 prospective, nonrandomized study of weekly adjuvant paclitaxel in combination with trastuzumab (APT) for 12 weeks, followed by maintenance trastuzumab for 1 year in patients with node-negative HER2+ breast cancer measuring 3 cm or less.[11,12] A total of 201 of the 406 study participants had pT1a/bN0 breast cancers. The 3-year DFS in this group was 99.5%, a proportion significantly higher than the historical data from the MD Anderson series, among others. An ongoing randomized phase 2 trial (ATEMPT Trial) is comparing the Dana-Farber APT regimen with the immunoconjugate ado-trastuzumab emtansine (T-DM1) given every 3 weeks for 17 cycles for patients with HER2+ stage I breast cancer.[13] The primary end points of this trial are DFS (assessed at 2 years) and safety, and the design calls for a 3:1 randomization favoring T-DM1 and an accrual of 500 patients.

Adverse Reactions of HER2-Targeted Therapy

Cardiac events are the adverse events (AEs) of greatest concern for HER2-targeted therapy, especially when small benefits in outcome are projected. Pivotal trials of HER2-targeted therapies have shown heterogeneity in their definitions of cardiac AEs, but each trial consistently reported an increase in cardiac AEs.[14,15] In the NSABP-B31 and NCCTG-N9831 trials, the cumulative incidence of congestive heart failure at 7 years of follow-up was 4% with trastuzumab given concurrently with chemotherapy and after anthracycline compared with 1% with chemotherapy alone.[14] In the HERA trial that used trastuzumab following all chemotherapy, the incidence of New York Heart Association (NYHA) III/IV congestive heart failure was 0.8% compared with 0% in the control group, and 5.2% of patients had to discontinue trastuzumab due to cardiac AEs.[15] Templeton et al conducted a pooled analysis of these pivotal trials showing an absolute increase of 1.8% for grade 3 or 4 cardiac toxicity (2.1 vs 0.3%), with an odds ratio of 7.6 (95% CI, 4.4-13.1; *P* <.001).[16] Cardiac AEs are more likely following prior use of anthracycline. This was shown in the BCIRG-006 trial where congestive heart failure and cardiac dysfunction were significantly more common in the group receiving AC-TH (2.0%) than the group receiving TCH (0.4%; *P* <.001) or AC-T (0.7%).[9] Although most cardiac AEs are reportedly transient, the BCIRG-006 trials demonstrated a significant difference in sustained, subclinical loss of mean LVEF (defined as >10% relative loss) in the group receiving AC-TH (18.6%) compared with AC-T (11.2%) and TCH (9.4%) (*P* <.001).[9] In the APT trial, Tolaney et al reported that only 2 patients (0.5%) developed symptomatic congestive heart failure after treatment with paclitaxel/trastuzumab combination, and both cases resolved after discontinuation of trastuzumab.[11]

In addition, trastuzumab is associated with infusion reaction in up to 40% of patients.[17] Other common adverse reactions include diarrhea and infection.

Toxicities reported from clinical trials may underestimate AE rates, as they tend to enroll healthier and more highly resourced patients. A population-based retrospective study showed a 5-year cumulative incidence of heart failure as high as 20% (95% CI,

14-25.6%) in patients treated with anthracycline and trastuzumab.[18] In the SEER-Medicare data review, 2028 patients 66 years or older were included. Among these patients, 1.2% and 1.7% were hospitalized with heart failure during trastuzumab treatment and in the year after treatment, respectively. Patients who had a history of cardiac disease had a higher likelihood of requiring a cardiac admission during treatment (9.6% vs 2.7%; $P < .001$).[19]

Cost-Effectiveness

It is estimated that a year of adjuvant trastuzumab alone will cost $57,000. This does not include the additional cost of cytotoxic partner drugs, surveillance, management of cardiac toxicity, physician visits, and travel expenses.[20] Although adjuvant trastuzumab in HER2+ breast cancer is undoubtedly cost-effective,[21,22] it is unclear whether the cost-effectiveness extends to pT1a/bN0M0 HER2+ tumors given the overall low recurrence risk and small impact on outcome. In the face of rising healthcare costs, the cost-effectiveness of adjuvant trastuzumab therapy in patients with pT1a/bN0M0 HER2+ breast cancer is a significant consideration that will require further analysis and modeling of available and pending data.

Conclusion

Although pT1a/bN0M0 breast cancers are associated with favorable prognosis, HER2 overexpression in these patients certainly carries a worse prognosis with more distant recurrences and lower OS rates. HER2 overexpression has been associated with a DFS as low as 67%[5] and as high as 100%.[4] It is challenging to make an accurate prognosis of this group of patients due to the lack of robust data. Which factors contribute to the large difference in reported prognosis is unclear. A higher histological grade, negative hormone–receptor status, and/or the larger tumor size associated with HER2 positivity have been cited as possibilities. Fehrenbacher reported that T1b tumors measuring 1 cm clearly had worse DRFI compared with other pT1a/bN0M0 HER2+ breast cancers.[6] Adjuvant trastuzumab has been associated with excellent survival,[10-12] but the benefit attributable to trastuzumab has not been confirmed, nor has the magnitude of the benefit been estimated in a randomized trial. Given the overall good prognosis in this group of patients, the absolute benefit from adjuvant HER2-targeted therapy is likely small. Thus, the decision for treatment should entail a discussion of risk and benefit between the physician and patient, especially patients with T1b breast cancers with poor risk features (eg, tumors measuring 1 cm, high histological grade, and/or hormone receptor–negative status). This discussion could include benefit estimated using the natural history of untreated pT1a/bN0 HER2+ cancers. Moving forward, we will need a more reliable method to identify patients with high-risk pT1a/bN0M0 HER2+ who will benefit from treatment. Perhaps the 70-gene expression profile assay (Mammaprint) could be a useful tool, as the validation of this assay included HER2+ tumors, such that low-risk hormone receptor–positive tumors could be recommended for adjuvant hormonal therapy alone. However, this assumption should be tested using data from past or ongoing trials. In addition to benefit prediction assays, regimens with a more favorable toxicity profile, ideally nonanthracycline-based or even chemotherapy-free, need to be evaluated in order to improve the risk-benefit ratio for this category of patients.

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Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Advanced Non-Small Cell Lung Cancer

A paradigm shift in stage IV non-small cell lung cancer treatment

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Abstract

Epidermal growth factor receptor (*EGFR*) mutations act as oncogenic drivers in the cellular signal transduction pathway and induce downstream activation of several key cellular events involved in cellular proliferation and survival. This review is aimed at summarizing the existing knowledge on the role of EGFR in cellular signal transduction, how *EGFR* mutations act as oncogenic drivers in advanced non-small cell lung cancer (NSCLC), current clinical studies of approved EGFR tyrosine kinase inhibitors (TKIs) in the treatment of advanced NSCLC, the development of EGFR TKIs resistance and its management, and future directions in the field.

Key words: EGFR, TKIs, NSCLC, lung cancer

Introduction

Lung cancer is the leading cause of cancer-related death in both men and women in the United States, and the median 5-year survival rate for lung cancer is 5% worldwide.[1] Lung cancer is divided into 2 major categories based on histological features: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), which constitute 15% and 85% of lung cancer cases, respectively. Most patients with NSCLC are diagnosed with advanced and unresectable disease (stage IIIB or IV). If left untreated, these patients have a median survival of less than 6 months. The initial standard treatment regimen usually includes a doublet of platinum agents and a taxane. In a landmark study of 1207 patients with advanced NSCLC, treatment with any of 4 doublets resulted in similar outcomes in radiological response (19%) and overall survival (OS; 7.9 months).[2] One promising strategy to improve survival in these patients involves targeting the epidermal growth factor receptor (EGFR) in advanced NSCLC.

In 1986, Stanley Cohen won the Nobel Prize for his discovery of the epidermal growth factor.[3] Its receptor was isolated in 1988 when Mendelsohn and colleagues first suggested EGFR as an anticancer target.[4] It was not until May 2004 that 2 pivotal studies showed the correlation between somatic mutations in the kinase domain of EGFR and the strong response of advanced NSCLC to EGFR tyrosine kinase inhibitors (TKIs).[5,6] These landmark studies opened a new chapter of targeted therapy and a new treatment paradigm in the management of advanced NSCLC.

The Biology of *EGFR* Mutations and Their Role in Intracellular Signaling

EGFR, also referred to as ErbB1, is 1 of 4 receptors collectively described as the receptor tyrosine kinases (RTKs) of the ErbB family. Other members of this family of receptors include ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4). All have a common structural architecture comprising an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain with tyrosine kinase activity for signal transduction. The binding of its ligand to EGFR initiates a cascade of intracellular signaling that ultimately leads to the expression of the cellular effects in the form of cell proliferation and survival.

EGFR mutations as a major and potent oncogenic driver of advanced NSCLC were first described independently by Lynch et al[5] and Paez et al[6] when gefitinib, one of the first EGFR TKIs designed to target the intracellular tyrosine kinase domain of EGFR, was demonstrated to cause dramatic tumor reduction in selected patients with *EGFR* mutations.

The 2 most common *EGFR* mutations in NSCLC are the L858R mutation in exon 21 and the exon 19 deletions. Both are drug-sensitizing mutations and together represent 85% to 90% of *EGFR* mutations in lung cancer. Exons 18 to 21 encode a portion of the tyrosine kinase domain of EGFR, and the most common alteration occurs as a T to G mutation at nucleotide 2,573 in exon 21, leading to substitution of arginine for leucine at position 858 (L858R). In the exon 19 deletants, there is a deletion of 4 amino acids (LREA).[5]

The biochemical mechanism of EGFR kinase domain mutation activation results from an increased and sustained duration of receptor activation (gain-of-function) by the ligands compared with wild-type *EGFR*.[5] Kinetic analysis of the purified intracellular domain of *EGFR* L858R and a representative deletion mutant showed that both mutants displayed a higher Michaelis con-

stant (Km) (substrate concentration at which the reaction rate is half of V_{max}) for ATP and a lower dissociation constant (Ki; the measure of ligand binding affinity) for erlotinib relative to the wild-type receptor, leading to a 100-fold difference in sensitivity to EGFR TKIs.[7,8] Mutations in the EGFR tyrosine kinase are observed in approximately 15% of NSCLC adenocarcinomas in the United States and occur more frequently in women and nonsmokers.[9] The incidence in East Asian populations is 22% to 62%.[10]

EGFR mutations with del 19 and L585R are referred to as gain-of-function mutations because they cause activation of the EGFR signaling pathway in the mutant *EGFR*-positive oncogenic cells, and some of these mutations also lead to greater sensitivity to EGFR TKIs compared with cases with wild-type EGFR. Resistance mutations also occur either de novo or following prolonged exposure to EGFR TKIs. Examples of the primary resistance *EGFR* mutations include the *KRAS, PTEN,* and *BRAF* mutations, all of which confer resistance to EGFR TKIs in NSCLC tumors with these mutations**.** The T790M mutation in the *EGFR* gene can be either primary or acquired, while *MET* amplification and epithelial-mesenchymal transition (*EMT*) are both acquired mutations conferring resistance to EGFR TKIs.

Other mutations in advanced NSCLC tumors are collectively described as uncommon *EGFR* mutations of unknown clinical significance; their number is small compared with the well-described *EGFR* mutations of clinical significance. These mutations in the *EGFR* involve amino acid substitution in E709, G719, S768, L861, and others. Their association to the effectiveness of the EGFR TKI is currently not well understood.[11,12] However, a recent study by Wu et al[13] showed that mutation on G719 and L861 comprised a major part (28 of 62) of the uncommon mutations and were associated with a favorable effectiveness of EGFR TKIs, while mutations other than these 2 led to a worse response to EGFR TKIs. This study concluded that uncommon *EGFR* mutations constitute a distinct part of the whole group of *EGFR* mutations, that their composition was heterogeneous, and that their association with EGFR TKIs differed.[13]

Diagnostic Testing in *EGFR* Mutation–Positive NSCLC

Since the discovery of *EGFR* mutations and other clinically significant molecular aberrations in NSCLC, a number of diagnostic tests have been developed to assay for these genomic alterations. As advancement in this field had culminated in the development of multiple highly sophisticated genomic sequencing technologies, it is imperative to have a firm understanding of the various options and the institutional guidelines available in selecting the appropriate test in the office practice. In an October 2014 press release, the American Society of Clinical Oncology (ASCO) announced its endorsement of the clinical practice guideline on molecular testing for selection of patients with lung cancer for therapies targeting EGFR and anaplastic lymphoma kinase (ALK), developed by the joint College of American Pathologists (CAP)/International Association for the Study of Lung Cancer (IASLC)/Association for Molecular Pathology (AMP).

The guidelines recommend that testing should be offered at the time of diagnosis for patients with advanced NSCLC or recurrence regardless of tumor size or patient characteristics, such as gender, race, and smoking status. Although the guideline did not identify a specific testing platform, it recommends against assays that utilize immunohistochemistry (IHC) for *EGFR* and *EGFR* copy number and mutation analysis, except for samples that are insufficient for molecular analysis. It also advises laboratories to set a minimal cellularity requirement during assay validation for EGFR testing and recommends that the exact method chosen should be able to identify *EGFR* mutations in samples with more than 10% tumor cells. For the detection of acquired resistance *EGFR* mutations such as T790M, the testing should be adequately sensitive in samples with more than 5% tumor cells. There was also stipulation placed on the operationalization for the testing laboratories to ensure that results are made available within 5 to 10 workdays, with transportation times of 3 days for external facilities and 24 hours for institution-based laboratories.[14] The guidelines also recommend molecular testing for *ALK*-rearrangement in all patients with advanced NSCLC to ensure that all patients who are candidates for ALK-targeting therapies, such as crizotinib and certinib, are identified.[14] The currently available range of molecular testing platforms for EGFR testing in laboratories include Sanger sequencing, IHC, multiplex hotspot mutation testing, multiplex sizing assays, and next-generation sequencing.[15]

EGFR TKIs in the Treatment of NSCLC

Clinical oncologists have traditionally made treatment decisions based on the histology of lung tumors, distinguishing NSCLC from SCLC. In 2003, gefitinib, a first-generation EGFR TKI, received accelerated approval from the FDA as a second-line treatment for advanced NSCLC after two phase 2 trials (IDEAL-1 and -2) in chemotherapy-refractory patients demonstrated a response rate (RR) of 10% in Caucasian cohorts and 28% in Japanese cohorts.[16,17] Overall survival was 6 to 8 months in unselected patients.

Erlotinib was approved in 2004 after a phase 3 trial (BR.21) demonstrated that erlotinib monotherapy conferred a 2-month survival benefit over best supportive care (BSC) in patients with chemotherapy-refractory advanced NSCLC, with a RR of 9% in the erlotinib arm and less than 1% in the placebo arm.[18] Following the work of Lynch et al[5] and Paez et al,[6] who independently demonstrated *EGFR* mutations in some of the gefitinib responders, the apparently low RR in these studies was demonstrated to be related to the low incidence of *EGFR* mutations in the unselected patient populations. These studies demonstrated that the target of EGFR TKIs is *EGFR* with either a deletion

in exon 19 or a point mutation in exon 21, not in the wild-type receptor. Multiple phase 2 studies have confirmed the efficacy of the EGFR TKIs as second- and third-line therapy for *EGFR* mutation–positive NSCLC, and tumor response rates were shown to be consistently well over 60% independent of age, gender, and ethnicity.[19-21] A number of other phase 3 studies have validated the use of EGFR TKIs as first-line therapy in advanced NSCLC.[22-28]

EGFR TKIs as First-Line Therapy

The role of EGFR TKIs as first-line therapy in patients with *EGFR*-mutated advanced NSCLC was confirmed by the results of the randomized phase 3 IPASS (Iressa Pan-Asia) study.[23] In this trial, patients were enrolled based on clinical features to ensure good representation of the patient population with activating *EGFR* mutations, and tumor samples were analyzed retrospectively for presence or absence of *EGFR* mutations. *EGFR* mutation was confirmed as a predictive biomarker for response to EGFR TKIs by the results of this trial. Tumor RRs in patients with *EGFR* activating mutations were 71.2% in the gefitinib group compared with 47.3% in the chemotherapy arm, and were statistically significant (P <.001). The primary end point of progression-free survival (PFS) was significantly prolonged in the gefitinib treatment group (9.8 vs 6.4 months; hazard ratio [HR] = 0.48; P <.0001). An OS benefit could not be accounted for in the study because the majority of patients treated with first-line chemotherapy were crossed over to the gefitinib group at the time of progression.

The superiority of EGFR TKIs over standard platinum-based doublet chemotherapy was further supported by subsequent multiple trials that enrolled only patients with activating *EGFR* mutations and randomized them to either an EGFR TKI or chemotherapy (**Table**). Significantly higher RRs and prolonged PFS occurred consistently across all of the randomized studies, offering further support to the efficacy of EGFR TKIs as a standard treatment for patients with advanced NSCLC with *EGFR* mutations.

Afanitib, a second-generation TKI approved by the FDA in July 2013, is an irreversible EGFR TKI and is used as a first-line treatment option for patients with advanced NSCLC with *EGFR*

TABLE. Treatment Outcomes in EGFR-Mutated NSCLC: EGFR TKIs or Chemotherapy

Authors	Study	Arm	# of Patients	Tumor RR (%)	Median PFS (months)
Mok et al[23]	IPASS	Gefitinib vs Carbo/Paclitaxel	261	71.2 vs 47.3	9.8 vs 6.4
Han et al[27]	First-SIGNAL	Iressa vs Gem/Cis	42	84.6 vs 37.5	8.4 vs 6.7
Maemondo et al[73]	NEJ02	Gefitinib vs chemotherapy	114	73.7 vs 30.7	10.8 vs 5.4
Mitsudomi et al[28]	WJTOG 3405	Gefitinib vs Cis/Docetaxel	86	62.1 vs 32.2	9.2 vs 6.3
Zhou et al[20]	OPTIMAL	Erlotinib vs chemotherapy	154	83.0 vs 36.0	13.1 vs 4.6
Rosell et al[21]	EURTAC	Erlotinib vs chemotherapy	175	54.5 vs 10.5	9.4 vs 5.2
Sequist et al[24]	LUX-Lung 3	Afatinib vs Cis/Pemetrexed	345	56 vs 23	11.1 vs 6.9
Wu et al[25]	LUX-Lung 6	Afatinib vs Gem/Cis	364	66.9 vs 23	11.0 vs 5.6

Cis indicates cisplatin; Carbo, carboplatin; Gem, gemcitabine; EURTAC, Erlotinib versus Standard Chemotherapy as First-line Treatment for European Patients with Advanced EGFR Mutation-Positive Non-Small-Cell Lung Cancer; FIRST-SIGNAL, First-line Single Agent Iressa Versus Gemcitabine and Cisplatin Trial in Never-Smokers with Adenocarcinoma of the Lung; IPASS, Iressa Pan-Asia Study; LUX-Lung 3, Phase III Study of Afatinib or Cisplatin Plus Pemetrexed in Patients With Metastatic Lung Adenocarcinoma With EGFR Mutations; LUX-Lung 6, a Randomized, Open Label, Phase III Study of Afatinib Versus Gemcitabine/Cisplatin as First-line Treatment for Asian Patients With EGFR Mutation-Positive Advanced Adenocarcinoma of the Lung; NEJ, North East Japan; OPTIMAL, Randomised Phase III Study Comparing First-line Erlotinib versus Carboplatin Plus Gemcitabine in Chinese Advanced Non-Small-Cell Lung Cancer Patients with EGFR Activating Mutations; PFS, progression-free survival; RR, response rate; WJTOG, West Japan Thoracic Oncology Group.

mutations. It covalently bonds with the ATP binding sites of the tyrosine kinases, causing permanent inhibition to the site, and also has inhibitory effect on the HER2 receptor.

In a combined report of the phase 3 randomized LUX-Lung 3 and LUX-Lung 6 trials presented recently at the 2014 Multidisciplinary Symposium in Thoracic Oncology in Chicago by Sequist et al,[29] first-line afatinib was shown to improve OS in patients with advanced NSCLC with *EGFR* exon 19 deletion. In these trials, both of which shared the same design and methodology, patients with stage IIIB and IV NSCLC *EGFR*-positive mutations were randomized 2:1 to receive oral afatinib at a daily dosage of 40 mg or up to 6 cycles of pemetrexed/cisplatin in the LUX-Lung 3 trial and gemcitabine/cisplatin in the LUX-Lung 6 study. Randomization was stratified for both studies based on the mutation type (Del19/L858R/other), with 89% of patients in each trial possessing either del19 or L858R and 11% of patients having uncommon mutations. The patient population (N = 345) in the LUX-Lung 3 trial was stratified by race (Asian/non-Asian), with the non-Asians recruited from Europe, South America, and Australia. For the LUX-Lung 6 trial, the patient population (N = 364) was predominantly Chinese. The primary end point for both trials was PFS, which previously reported data showed was met by both trials.[24, 25] Secondary end points include OS, disease control rate (DCR), patient-reported outcome, and objective response rate (ORR). Median follow-up for OS was 40.9 months and 33.7 months for the LUX-Lung 3 and LUX-Lung 6 trials, respectively. The HR for OS was 0.78 (95% CI, 0.58-1.06; *P* =.109) versus pemetrexed/cisplatin and 0.83 (95% CI, 0.63-1.09; *P* = .176) versus gemcitabine/cisplatin. Results within the mutation subgroup were consistent between both trials. In the analysis of common mutation, OS improved in patients with *EGFR* del19 regardless of their race.

Data from LUX-Lung 3, comprising a global population, show a median OS of 33.3 months with afatinib versus 21.1 months with chemotherapy (HR = 0.54; 95% CI, 0.36-0.79). In LUX-Lung 6, comprising a primarily Asian population, the median OS was 31.4 months with afatinib compared with 18.4 months in the chemotherapy arm (HR = 0.64; 95% CI, 0.44-0.94). In LUX-Lung 3, the non-Asian population had a median OS of 33.6 months with afatinib compared with 20.0 months in the chemotherapy group (HR = 0.45; 95% CI, 0.21-0.95; *P* = .03). No significant difference in OS was seen in patients with L858R mutations between the afatinib and chemotherapy arms. However, the study authors concluded that despite the lack of clear differentiating factors between the regimens, afatinib remains a treatment option with *EGFR* L858R mutations, and that going forward, patients with these 2 mutations can no longer be grouped together in the same study because patients with del19 and L858R mutations behave quite differently.[29]

In an effort to determine which of the 3 currently available EGFR TKIs are best for treatment of advanced NSCLC with positive *EGFR* mutations, a phase 2 randomized study, LUX-Lung 7, is currently ongoing comparing afatinib with gefitinib as first-line therapy for patients with either exon 19 deletion or L858R mutations. Accrual for the study is completed, and results are pending.

EGFR TKIs as Second-Line Therapy

Prospective data comparing first- and second-line EGFR TKIs in patients with advanced NSCLC with activating *EGFR* mutations are limited and are usually based on single-arm studies. The largest of these prospective studies is the Spanish Lung Cancer Study Group, which reported on 113 chemotherapy-naïve and 104 chemotherapy-refractory patients.[17] In this trial, the tumor RR was 73.5% in the chemotherapy-naïve group and 67.4% in the chemotherapy-refractory arm, and the PFS was nearly the same between the groups (14 vs 13 months).

Another small prospective single-arm study from Japan, which evaluated the efficacy of first- and second-line EGFR TKIs, reported a RR of 77.8% in chemotherapy-naïve and 50% in chemotherapy-refractory patients.[30] Other data supporting the use of EGFR TKIs as second-line treatment came from a subgroup analysis of large randomized trials. For example, both the ISEL (Iressa Survival Evaluation in Lung Cancer) study and BR.21 (National Cancer Institute of Canada bronchogenic carcinoma study number 21) were conducted in unselected patient populations after progression on 1 or 2 lines of therapy. Patients were randomized to either an EGFR TKI or BSC.[18,31] In the ISEL study, only 26 patients with mutant *EGFR* received gefitinib, and the RR was 37.5%, while in the BR.21 study, 40 patients with the *EGFR* mutation treated with erlotinib showed a RR of 27%.

A recent study, the TAILOR trial (Tarceva Italian Lung Optimization Trial), compared the efficacy of erlotinib in patients with wild-type *EGFR* with that of docetaxel as a second-line therapy.[32] In this trial, patients with wild-type *EGFR* NSCLC at progression and who were previously treated with a first-line platinum-based regimen, were randomized to receive either erlotinib or docetaxel until disease progression or unacceptable toxicity occurred. Of the 222 patients evaluated (112 for erlotinib vs 110 for docetaxel), the median OS was 8.2 months (95% CI, 5.8-10.9) with docetaxel versus 5.4 months (range, 4.5-6.8 months) with erlotinib (adjusted HR = 0.73; 95% CI, 0.53-1.0; *P* = .05). PFS was significantly better with docetaxel than with erlotinib: median PFS was 2.9 months (95% CI, 2.4-3.8) with docetaxel versus 2.4 months (range, 2.1-2.6 months) with erlotinib (adjusted HR = 0.71; 95% CI, 0.53-0.95; *P* = .02). The study concluded that chemotherapy as a second-line therapy is more effective than erlotinib in previously treated patients with advanced wild-type *EGFR* NSCLC.

EGFR TKIs in Combination With Chemotherapy

Initial attempts to employ EGFR TKIs in combination with

FIGURE. EGFR Signaling Pathway

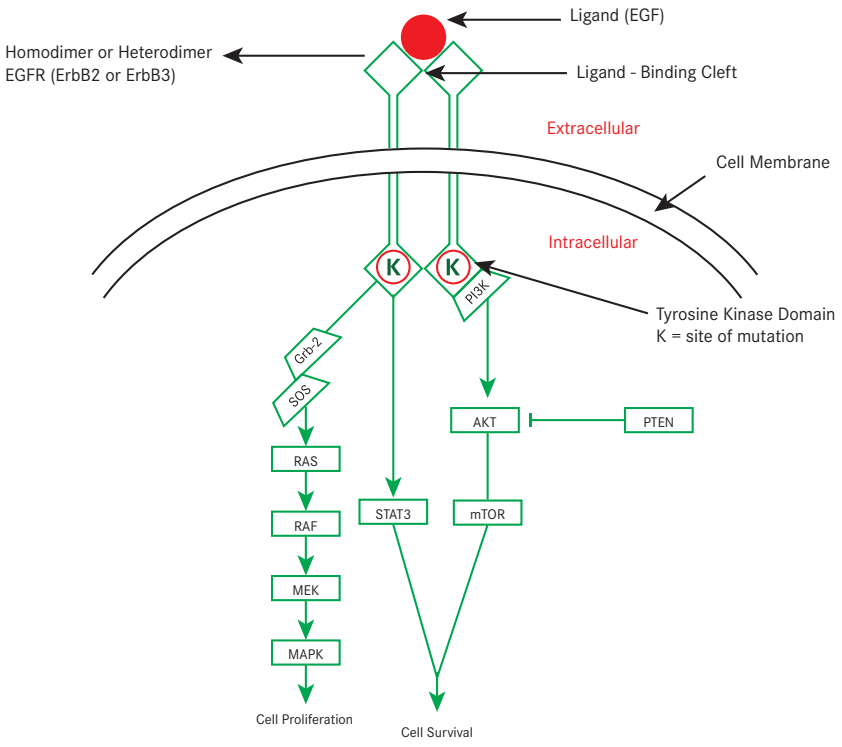

Figure showing the signaling pathway. TKIs block signaling at the tyrosine kinase domain (k). Resistance to TKIs occur when activating mutations occur downstream in KRAS or BRAF.

chemotherapy resulted in poor outcomes; multiple randomized studies that compared the combination of a platinum-based regimen plus an EGFR TKI with chemotherapy alone demonstrated a lack of benefit in the combination therapy group in unselected patient populations.[33-35] Due to the absence of detailed biomarker analysis from these studies, it was not clear whether the absence of benefit was related to the enrollment of a large number of patients with *EGFR* wild-type NSCLC who would derive minimal benefit from EGFR TKIs.

Preclinical studies were carried out to explore the possibility of a negative interaction between EGFR TKIs and chemotherapy when given concurrently. It was revealed in one of the studies that in NSCLC cell lines with activating mutant *EGFR* L858R, gefinitib caused apoptosis, while it only induced G1 cell cycle arrest in the wild-type *EGFR* cell lines.[36] The investigators speculated that this was due to the protective effect conferred on the accumulated tumor cell lines in the G1 phase by the EGFR TKIs, protecting them from the action of chemotherapy, which specifically targets cells in the S or G2 and M phases of the cell cycle. Other preclinical studies in NSCLC cell lines have shown the need for sequential administration of EGFR TKIs and chemotherapy by demonstrating that concurrent administration of erlotinib and an M phase–specific taxane results in lower levels and a sustained shorter duration of apoptosis when compared with the sequence of taxane followed by erlotinib.[37, 38]

In a retrospective analysis in the TRIBUTE trial (a phase 3 study of erlotinib combined with paclitaxel and carboplatin), patients with wild-type *EGFR* tumors who received combination erlotinib and chemotherapy had higher rates of progressive disease and inferior survival compared with patients who received chemotherapy alone.[39] This was also true for patients with activating *EGFR* mutations who received combination therapy or chemotherapy alone.

Based on the results of TRIBUTE, 2 studies were launched in Asia to investigate the role of intercalated chemotherapy with erlotinib. The first was FASTACT (First-line Asian Sequential Tarceva and Chemotherapy Trial), a multicenter randomized, placebo-controlled, phase 2 trial comparing the intercalated combination of chemotherapy (gemcitabine 1250 mg/m^2 on days 1 and 8) and erlotinib (days 15-28) with chemotherapy alone in unselected patient populations with advanced NSCLC.[40] Results from the study showed a significantly improved PFS (HR = 0.57; log-rank P = .018). FASTACT 2, a phase 3 trial, was based on the result of FASTACT with the same study design (N = 451).[41] Approximately 85% of patients in the placebo group received second-line erlotinib on progression; this ensured that the *EGFR* mutation–positive subgroup had adequate exposure to an EGFR-TKI. Results from this trial showed the median PFS was 7.6 months in the combination group compared with 6.0 months in the chemotherapy alone group (HR 0.57; 95% CI, 0.47- 0.69; P ≤.0001). The median OS was 18.3 months versus 15.2 months (HR 0.79; 95% CI, 0.64- 0.99; P = .042), also favoring the combination group. Biomarkers analysis was done in 240 patients, and 97 (40%) had EGFR mutations. The survival benefit for the intercalated combination following subgroup

analysis was restricted to patients with activating EGFR mutations, but not patients with wild-type EGFR tumors. There was a remarkable improvement in the *EGFR* mutation–positive subgroup, with over 10 months of improvement in the median PFS and OS. These results will need further confirmation before the approach can be recommended outside of a formal clinical trial.

Resistance to EGFR TKIs

Primary resistance to EGFR TKIs occurs when tumors do not undergo significant shrinkage in response to gefitinib and erlotinib in EGFR TKI-naïve patients on first exposure. Multiple mechanisms are believed to be involved. One of these was demonstrated by Greulich et al[42] in a preclinical study and later reported by Wu et al[43] in retrospective clinical data, both demonstrating that tumors with exon 20 insertions are generally insensitive to EGFR TKIs. This occurs in less than 5% of patients with NSCLC. In about 20% of NSCLC cases, primary resistance is mediated by mutation in the KRAS signaling protein.[44] An *EGFR* mutation is more common in never-smokers, while the *KRAS* mutation is prevalent in former and current smokers; their occurrences are mutually exclusive. Other implicated but rare mutations in primary resistance to EGFR TKIs include *PTEN, MEK,* and *ALK*-fusion.[45-47]

Acquired resistance eventually develops in all patients with *EGFR* mutation–positive advanced NSCLC treated with gefitinib and erlotinib despite their substantial efficacies. Disease progression usually appears after about 1 year of treatment with either drug.[48,49] The most common acquired resistance results from the T790M mutation, in which a C to T change occurs at the nucleotide 2,369 in exon 20 leading to substitution of methionine for threonine at position 790. The T790M residue lies within the drug-binding cleft of the EGFR and is thought to impair binding of the TKIs to the ATP binding site.[50] As an alternative mechanism, Yun et al[51] suggested that the amino acids change could alter the relative affinity of ATP versus drug. The EGFR exon 20 T790M mutations constitute 50% to 65% of acquired resistance to EGFR TKIs, and overlapping mechanisms are rare.[52-54]

Another well-defined separate mechanism of acquired resistance to EGFR TKIs is the amplification of *MET*, the gene encoding a different membrane-bound RTK.[55] *MET* amplification occurs regardless of the T790M status, and its amplification in cells originally dependent upon mutant *EGFR* illustrates a phenomenon that can be described as "kinase switch," in which surviving *EGFR* mutation–positive oncogenic cells exposed to prolonged action of EGFR kinase inhibition develop resistance by becoming dependent on another kinase, such as MET. Analysis of tumor samples and follow-up studies from multiple independent patients with *EGFR* mutation–positive NSCLC suggests that the prevalence of *MET* amplification may be closer to 10%.[56]

Other rarer forms of acquired resistance that have been described but not completely understood include activating *PIK-3CA* mutation,[57] transformations to SCLC,[58] activation of insulin-like growth factor receptor pathway,[59] and epithelial-mesenchymal transition (EMT).[60] The exact frequencies of these mechanisms have not been completely established.

Management of NSCLC With Acquired Resistance to EGFR TKIs

One modality of treatment in acquired resistance to EGFR TKIs is the use of local therapies, including radiotherapy, local ablation, and surgery if the sites of progression are limited. In a study by Yu et al,[52] local therapy was offered to 18 patients who progressed on an EGFR TKI; they reported a median time to systemic therapy of 22 months and a median OS of 41 months. Another retrospective study of 65 patients with 4 or fewer sites of progression (so-called "oligoprogression") while on an EGFR TKI or ALK inhibitor showed that local therapy could allow continuation of the TKI for more than 6 additional months.[61] A prospective comparative study will be required, however, before a local therapy can be considered as standard treatment. For now, it serves as an option for selective patients.

For systemic progression, platinum-based doublet chemotherapy is the standard option for treatment in patients with EGFR TKI-resistant advanced NSCLC who are chemotherapy-naïve. When there is metastasis to the brain, radiotherapy is the standard therapy. In a retrospective study of patients who had exposure to both chemotherapy and TKIs after the development of resistance, there was improvement in tumor RR: 41% versus 18% in favor of the doublet chemotherapy compared with the TKI group, but no significant differences in PFS or OS.[62] Patients who received platinum-based chemotherapy and erlotinib had a tumor RR of 63% compared with 23% in patients treated with doublet chemotherapy alone. Another small, single-arm, prospective study from Japan in patients treated with pemetrexed in combination with erlotinib or gefitinib after development of acquired TKI resistance showed a tumor RR of 26% and a median PFS of 7 months.[63]

However, results of The IMPRESS study (IRESSA Treatment Beyond Progression in Addition to Chemotherapy Versus Chemotherapy Alone),[64] a phase 3 randomized trial comparing combination pemetrexed/carboplatin and gefitinib with chemotherapy alone in *EGFR* mutation–positive patients who progressed on gefitinib, recently presented at the 2014 European Society for Medical Oncology (ESMO) Congress in Madrid, Spain, demonstrated no significant difference in RR and PFS (primary end point) between the treatment arms. The result showed an ORR of 31.6% for gefitinib versus 34.1% for chemotherapy alone. The disease control rate was 84.2% versus 78.2% respectively, and the median PFS was the same for both groups at 5.4 months.

The OS data are currently immature, with only 33% of required events; however, a preliminary report at the 2014 ESMO Congress was not encouraging either, with survival from time of randomization of 14.8 months with gefitinib versus 17.2 months with chemotherapy. The HR was 1.62, and the difference is potentially significant according to the report. No significant difference was observed between the treatments arms in rates of adverse events (AEs), serious AEs, and events leading to death. The report concluded that gefitinib should not be continued after disease progression by RECIST in patients with *EGFR* mutation–positive NSCLC on first-line gefitinib. A phase 2 study with a similar design is also currently in progress in the United States.

Another recently described EGFR TKI is AZD9291, a selective, third-generation EGFR TKI effective against EGFR TKI sensitizing and resistance T790M mutations in preclinical models. A phase 1 study presented at the 2014 ASCO Annual Meeting appears to show an encouraging outcome.[65] In this study, 199 patients with *EGFR* mutation–positive NSCLC with acquired resistance to EGFR TKIs were enrolled in a multicenter trial into dose escalation and expansion cohorts. Results as of January 16, 2014, in all evaluable patients, show a confirmed plus unconfirmed ORR (c+uORR) of 51%; RECIST responses were observed at all dosage levels and in brain metastasis. Among the 132 patients with centrally confirmed T790M mutation, the c+uORR in the 89 *EGFR* T790M-positive patients was 64% (95% CI, 53%-74%), and in the 43 *EGFR* T790M-negative patients, 23% (95% CI, 12%-39%). The overall DCR in T790M-positive patients was 96%. Among the 60 patients with confirmed response, 97% were ongoing at data cutoff and the longest duration of response as of the time of this report was more than 8 months. The conclusion from the report was that AZG9291 has an impressive efficacy and is well tolerated in patients with *EGFR* mutation–positive NSCLC with acquired resistance to EGFR TKIs. More trials on this agent, as well as trials of another T790M-targeting TKI (rociletinib, also known as CO-1686),[66] are currently ongoing. These third-generation TKIs may provide new options for acquired resistance to EGFR TKIs.

One other way of circumventing the effect of acquired resistance to EGFR TKIs currently under development is to indirectly target mutant *EGFR* by HSP90 inhibitors. HSP90 is a heat shock protein, which is required for stability and functioning of multiple signaling proteins that promote the growth and/or survival of cancer cells such as EGFR, MET, hepatocyte growth factor, and EML4/ALK. Analysis of the interaction between HSP90 and mutant *EGFR* has revealed that the mutant *EGFR* proteins are more dependent than their wild-type counterparts on HSP90 to fold properly; consequently, mutant *EGFR* is more sensitive to degradation following HSP90 inhibition with geldanamycins.[67] Further analysis of this mechanism has shown that HSP90 inhibitors induce stabilization or regression of T790M+ *EGFR* tumors by enhancing the degradation of the mutant receptor and sensitize *EGFR*-mutant tumors to paclitaxel.[68-70] So far, clinical data have been disappointing for HSP90 inhibitor IPI-504,[71] but many more agents are currently under various stages of clinical trials, for which preliminary reports are forthcoming.

Dual targeting of EGFR kinase domain in patients with an acquired resistance to EGFR TKIs is also being explored. One example is a recently reported result of a phase 1 dose escalation and expansion trial involving dual therapy with anti-EGFR monoclonal antibody cetuximab and afatinib.[72] In this study, an ORR of approximately 30% was reported; however, this optimistic result was tempered by the continued presence of toxicities, with as many as 69% and 77% of patients experiencing diarrhea and rash of any grade, respectively.

Future Directions and Conclusion

The past decade has seen an exciting paradigm shift in the management of advanced NSCLC with the development of gefitinib and erlotinib, the approval of a second-generation TKI, and third-generation TKIs currently undergoing various levels of clinical trials. The discovery of *EGFR* mutation as an important determinant of NSCLC response to TKIs has yielded a better outcome in patients with advanced NSCLC with *EGFR* mutations. This development has enabled clinicians to stratify patients according to the type of genetic mutations expressed by their NSCLC cells instead of their histological types alone, and this has made the prospect of personalized medicine more of a reality. With additional research in the study of tumor cell genomics and genetic abnormalities driving the growth of cancer cells, in the near future we hope to be able to characterize more patients according to the genetic expression driving the growth of their tumors and tailor their management by exploiting these mutations for therapeutic benefit in many more cancer types. Above all, there is an optimistic expectation that advanced-stage *EGFR*-positive NSCLC—even though it is incurable—may be managed as a chronic disease in the future.

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Advancements in Recurrent and Metastatic Cervical Cancer

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Abstract

Cervical cancer is the third most common cancer in women worldwide; however, the prognosis of advanced, recurrent, or metastatic cervical cancer remains poor. Several chemotherapy regimens have some activity in advanced cervical cancer; nevertheless cisplatin and paclitaxel are still considered the most effective treatments and the standard of care. The addition of bevacizumab in combination with chemotherapy has shown improved overall survival in phase 3 studies, resulting in approval by the FDA in 2014. Other targeted agents have shown limited activity so far. Immunotherapy is emerging as a promising treatment for cervical cancer. We review the literature behind bevacizumab as a single agent, bevacizumab in combination chemotherapy, and promising targeted therapies in advanced and recurrent cervical cancer and their implications in clinical practice.

Key words: cervical cancer, bevacizumab, targeted therapy

Introduction

Cervical cancer is the third most common cancer in women worldwide and is diagnosed in over 12,000 women in the United States each year.[1] Among minorities, cervical cancer has increased in incidence each year, with a global annual death rate of 275,000.[2] Worldwide it remains one of the most common causes of cancer death among women. The human papilloma virus (HPV) is the primary cause of cervical cancer worldwide, and is implicated in over 99% of cases.[3]

Progress in the management of cervical cancer has been slow. Over the last 60 years, 2 major advances were accomplished. First, the introduction of the PAP smear as a screening method in the 1950s, which led to a 60% or higher decrease in death from cervical cancer.[4] Second, though 50 years later, several randomized trials demonstrated a 30% to 60% reduction in the risk of death with the addition of cisplatin to radiation therapy, which led the National Cancer Institute to issue a clinical alert.[5]

Current treatment for cervical cancer can yield cures in 80% to 90% of women with early stage I and II cervical cancer and 60% in stage II. However, the prognosis for women with advanced or recurrent cervical cancer remains poor.[6] More recently, the development of targeted therapies that selectively target specific molecular pathways involved in tumorigenesis may lead to other major advances in the management of cervical cancer. We review the literature behind current and emerging therapies in advanced and recurrent cervical cancer and their role in clinical practice.

The Effect of Chemotherapy in Cervical Cancer

For the vast majority of patients with recurrent or metastatic disease, chemotherapy has represented the only treatment option. However, it is important to remember that in patients with limited metastatic disease in the para-aortic nodes, central pelvic recurrences, or solitary lung metastasis, long-term survival can be achieved with surgical resection and\or radiation therapy.[5-12]

Several chemotherapy agents have activity in previously untreated advanced cervical cancer. Traditionally, cisplatin has been considered the most active drug.[13] Other agents with documented activity include ifosfamide, paclitaxel, topotecan, irinotecan, capecitabine, and pemetrexed.[14-19] Current evidence suggests that platinum-based combination regimens may be more effective. The combination of cisplatin and paclitaxel yields a higher response rate and improved progression free survival (PFS) compared with single-agent cisplatin but does not improve overall survival (OS).[20] However, there are potential benefits to quality of life. The combination of cisplatin and topotecan compared with single-agent cisplatin showed an improvement in overall response rate (ORR), PFS, and OS.[21] On the other hand, the toxicities were significant, with 78% of patients in the study requiring unanticipated hospital admissions for supportive care and management of toxicities.[17]

The efficacy of 4 platinum-based doublets was evaluated in a large randomized trial.[22] Patients were randomly assigned to cisplatin in combination with either paclitaxel, vinorelbine, gemcitabine, or topotecan. This study reported that vinorelbine, gemcitabine, and topotecan were not superior to paclitaxel in

terms of OS, although a trend in response rate (RR), PFS, and OS favored paclitaxel.

Due to its more favorable toxicity profile, the combination of carboplatin plus paclitaxel could be a reasonable alternative to paclitaxel. In an unpublished phase 3 randomized trial, 253 women with recurrent or metastatic cervical cancer were treated with paclitaxel or carboplatin and paclitaxel.[23] Overall no significant differences were observed in PFS (6.9 months vs 6.21 months; hazard ratio [HR], 1.04; 95% CI, 0.80-1.35) or OS (18.3 months vs 17.5; HR, 0.99; 90% CI, 0.79-1.25; noninferiority $P = .032$). Paclitaxel was associated with more febrile neutropenia (16% vs 7.3%), grades 2 through 4 nausea and vomiting (36.8% vs 23%), and increased serum creatinine grades 2 through 4 (9.6% vs 4.8%). Carboplatin and paclitaxel was associated with more arthralgias (22.2% vs 11.2%), myalgias (16.7% vs 7.2%), motor neuropathy (8% vs 4%), and sensory neuropathy (27% vs 14.4%). It should be noted though, that in women not previously treated with cisplatin, carboplatin plus paclitaxel resulted in a much lower median OS compared with the standard doublet of cisplatin and paclitaxel (13 vs 23 months; HR, 1.57; 95% CI, 1.06-2.32; $P = .838$). Therefore, in platinum-naïve patients, a cisplatin-based regimen is still the preferred treatment of choice with a superior response rate compared to carboplatin. The results of these studies are summarized in **Table 1**.

Treatment options after first-line platinum-based therapy are limited. Many chemotherapy agents and several targeted agents have been evaluated, but in general have limited activity. Topotecan, vinorelbine, and pemetrexed are among the most active agents, while docetaxel, gemcitabine, vinorelbine, erlotinib, cetuximab, sunitinib, lapatinib, and pazopanib were found to have minimal activity.[24-33] The results of these studies are summarized in **Table 2**.

Novel Agents

Bevacizumab

The most promising experimental therapy to date in cervical cancer is targeting angiogenesis to block the growth of nutrient-supplying blood vessels in cancerous tumors with the vascular endothelial growth factor (VEGF) inhibitor bevacizumab. A phase 2 multicenter trial evaluating single-agent bevacizumab therapy among women with persistent or recurrent squamous cell carcinoma of the cervix was reported.[34] Study participants consisted of 46 patients with measurable disease who had been treated with no more than 1 or 2 non–cisplatin-based cytotoxic regimens or any prior cisplatin-based chemotherapy, and had good performance status, with adequate hematologic, renal, hepatic, and coagulation function. The median age was 46 years. Most patients were Caucasian (69.6%). Almost half (47.8%) had a Gynecologic Oncology Group (GOG) performance status of 0. The most common histology (93.5%) was squamous cell carcinoma. All patients had at least 1 prior chemotherapy regimen. The majority of the patients had prior radiation (82.6%) and prior hysterectomy (56.5%). The median duration of response was 6.21 months (range, 2.83 to 8.28 months). The median PFS and OS times were 3.40 months (95% CI, 2.53-4.53 months) and 7.29 months (95% CI, 6.11-10.41 months), respectively. Five patients

TABLE 1. Phase 3 Randomized Trials of Frontline Therapy for Advanced Cervical Cancer

Author	Treatment	N	ORR (%)	PFS (months)	*P*	OS (months)	*P*
Miller[26]	Cisplatin	134	19	2.8	<.001	8.8	NS
	PC	130	36	4.8		9.7	
Long[21]	Cisplatin	146	13	2.9	.014	6.5	.021
	Topotecan/Cisplatin	147	27	4.6		9.4	
Monk[22]	PC	103	29.1	5.82		12.87	
	VC	108	25.9	3.98	.06	9.99	.71
	GC	112	22.3	4.7	.04	10.28	.90
	TC	111	23.4	4.57	.19	10.25	.89
Tewari[37]	Chemotherapy	225	36	5.9	.002	13.3	.004
	Chemotherapy/Bevacizumab	227	48	8.2		17.0	
Kitagawa[23]	PC	121	-	6.9	.053	18.3	.032
	Carboplatin/Paclitaxel	123	-	6.21		17.5	

GC indicates gemcitabine/cisplatin; NS, not stated; ORR, objective response rate; OS, overall survival; PC, paclitaxel/cisplatin; PFS, progression-free survival; TC, topotecan/cisplatin; VC, vinorelbine/cisplatin.

TABLE 2. Second-Line Therapy for Advanced Cervical Cancer

Author	Agent	N	ORR (%)	PFS (months)	OS (months)
Bookman[24]	Topotecan	45	12.5	2.1	6.6
Muggia[25]	Vinorelbine	44	13.7	NS	NS
Miller[26]	Pemetrexed	29	15	3.1	7.4
Lorusso[27]	Pemetrexed	43	13.9	10 weeks	35 weeks
Garcia[28]	Docetaxel	27	8.7	3.8	7.0
Schilder[29]	Gemcitabine	22	4.5	2.1	6.5
Mackay[30]	Sunitinib	19	0	3.5	NS
Monk[31]	Lapatinib	78	5	17.1 weeks	39.1 weeks
	Pazopanib	74	9	18.1 weeks	50.7 weeks
Schilder[32]	Erlotinib	28	0	1.87	4.96
Santin[33]	Cetuximab	38	0	1.97	6.7
Monk[34]	Bevacizumab	46	10.9	3.4	7.29

NS indicates not stated; OS, overall survival; ORR, objective response rate; PFS, progression-free survival.

(10.9%) had partial responses. Grade 3 or 4 adverse events (AEs) included hypertension (n = 7), thromboembolism (n = 5), gastrointestinal (n = 4), anemia (n = 2), other cardiovascular (n = 2), vaginal bleeding (n = 1), neutropenia (n = 1), and fistula (n = 1). One death occurred due to infection. The study suggested that the activity of single-agent bevacizumab compared favorably with cytotoxic chemotherapy drugs.

Bevacizumab in Combination With Chemotherapy

Since 2006, small studies have suggested that the combination of bevacizumab and chemotherapy was highly active in advanced cervical cancer.[35,36] However, the most significant and practice-changing study for the management of advanced cervical cancer was recently reported by the GOG. In protocol GOG 240, women diagnosed with recurrent, persistent, or metastatic cervical cancer who had no prior chemotherapy except for chemotherapy used concurrently with radiation therapy for locally advanced nonmetastatic disease, were enrolled into a phase 3 randomized study.[37] A total of 452 women were enrolled into a factorial 2 × 2 design study where approximately half the patients received topotecan with paclitaxel and the other half received cisplatin and paclitaxel. Additionally, about half of the patients in each of these treatment groups received bevacizumab with their chemotherapy. The addition of bevacizumab to combination chemotherapy was associated with an improvement of 3.7 months in median OS (**Table 1**). The difference in OS translated into an HR for death of 0.71 in favor of the addition of bevacizumab (P = .004). Response rates were 48% with bevacizumab and 36% with chemotherapy alone (P = .008). There was significantly more toxicity in patients who received bevacizumab. However, this represented the usual toxicities associated with bevacizumab. Grade 2+ hypertension was seen in 29% of patients versus 2% in those who received chemotherapy alone. Grade 3+ thromboembolic events occurred in 8% of bevacizumab-treated patients and 1% of patients who received only chemotherapy. Grade 3+ gastrointestinal fistula occurred in 3% of the bevacizumab group but in none of the patients who received chemotherapy without bevacizumab. Despite the toxicities, the addition of bevacizumab showed acceptable safety, and patients did not report a statistically significant decrease in patient-reported quality of life. As a secondary outcome in the study, topotecan-paclitaxel did not outperform cisplatin-paclitaxel, even among patients with prior exposure to cisplatin. The study did not distinguish the differences in toxicity profile between the combination chemotherapy regimens. However based on previous trials, it is expected that the use of topotecan-paclitaxel causes more fatigue, leukopenia, and neutropenia, and significantly more thrombocytopenia and anemia compared with cisplatin-paclitaxel.[23]

Emerging Therapies

As mentioned, except for bevacizumab, the role of other targeted therapies in cervical cancer so far remains undetermined. However, it is important to remember that these trials have typically been conducted in a nonenriched patient population. In terms of chemotherapy agents, there has been renewed interest in the potential role of fluoropyrimidines. Several trials have reported modest activity for single-agent capecitabine.[18,38,39] Recently encouraging activity was reported in a phase 2 study with S-1.[40] S-1 is an oral fluoropyrimidine consisting of tegafur, a prodrug of 5-fluorouracil, gimeracil, an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil, and oteracil, which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the gastrointestinal toxic effects of fluorouracil. In this study, 36 patients received a median of 4 cycles with an ORR of 30.6%. The median time to progression and the median survival time were 5.2 and 15.4 months, respectively. These promising results have led to a randomized phase 3 study evaluating the efficacy and safety of S-1 with cisplatin versus single-agent cisplatin in patients with stage IVB, recurrent, or persistent carcinoma of the cervix.[41]

Immunotherapy

There have been significant advances in the past several years with regard to immunotherapy for cancer, beginning a new era of research in oncology. By identifying T cells that target cervical cancer HPV oncoproteins, and enriching for and expanding

these T cells ex vivo, efforts are being made to attack cervical tumors that have not been immunologically targeted before. The hope is that immunotherapy and adoptive T-cell therapy can induce regression of cervical cancer.

A novel study investigated use of human papillomavirus-targeted tumor-infiltrating lymphocyte therapy.[42] In this ongoing study, T cells were harvested from tumor tissue and cultured. The cultures were then tested for HPV viral protein E6 and E7 reactivity. The most reactive cultures were selected for infusion and then expanded. Billions of these expanded T cells were then infused into the patient. Nine patients have received tumor-infiltrating lymphocytes. One patient achieved partial response and 2 patients achieved a complete response. These complete responses were still ongoing at 22 months and 15 months after treatment. Most common toxicities included grade 3 and 4 myelosuppression, neutropenia, fever, and diarrhea. This study provided preliminary encouraging results, and completion of this study is eagerly awaited.

Another promising agent in development is live attenuated Listeria monocytogenes-based immunotherapy (ADXs11-01). ADXS11-001 is a drug that is designed to create a Th-1 type immunologic response, generating CD8+ T cells that target HPV-E7-transformed cells while simultaneously suppressing the immunologic tolerance within the lesions.[43] In a recent phase 2 study of ADXS11-001 in the treatment of persistent or recurrent cervical cancer, patients previously treated with chemotherapy, radiotherapy, or both were randomized to either 3 or 4 dosages of ADXS11-001 with cisplatin.[44] In the study, 18-month survival was 28% and 12-month survival was 36%. There was an 11% ORR, with an average duration of 10.5 months after 1 cycle of ADXS11-001. Prior therapy, baseline performance status, and the addition of cisplatin had no effect on survival or response. Current studies are needed to optimize the dosage and inclusion of multiple cycles with other agents to determine whether ADX11-001 can be used as an active agent against recurrent cervical cancer.

Based on these results, other immunotherapies such as nivolumab and ipilimumab are currently being evaluated in phase 2 trials.[45-48] Nivolumab and ipilimumab are monoclonal antibodies that target and block 2 different receptors that negatively regulate T-cell activation (PD-1 and CTLA-4, respectively), impacting the tumor's defense against the immune system and boosting the immune system's ability to fight the tumor. Inhibition leads to compromised activation and suppressed effector functions such as proliferation, cytokine secretion, and tumor cell lysis that block "immune checkpoints."

Discussion

The results of the GOG 240 were encouraging and resulted in improved oncologic outcomes, suggesting that the use of bevacizumab in combination with chemotherapy may become the standard of care for recurrent, advanced, or metastatic cervical cancer. As a consequence of this study, bevacizumab was approved by the FDA for use in cervical cancer in August 2014.

Additional studies are needed to determine whether bevacizumab is beneficial in combination with second-line chemotherapies or in patients with less advanced disease. Recently, Schefter et al published the complete results of RTOG 0417, exploring the safety and efficacy of the addition of bevacizumab to chemoradiation therapy.[49] This phase 2 study showed that treatment was well tolerated and encouraging efficacy results were reported. These results warrant further investigation regarding whether bevacizumab can be used in patients who are not chemotherapy naïve or have been diagnosed with earlier stage cancers.

Despite the strong evidence suggesting improved OS in patients who receive bevacizumab in addition to combination chemotherapy, there is a significant cost of bevacizumab that must be taken into account when providing treatment. The cost of chemotherapy plus bevacizumab may exceed $ 50,000. A cost-effectiveness decision model was recently published and reported that the cost of combined treatment was $53,784 compared with $5,688 for chemotherapy alone.[50] Therefore, the 3.7 month OS advantage with chemotherapy and bevacizumab came at an incremental cost-effectiveness ratio of $155K per quality-adjusted life year, which approaches common cost-effectiveness standards. Moderately discounting the cost of bevacizumab or using a lower dose significantly affects its affordability.

The role of immunotherapy is a promising and exciting new area of research that can potentially lead to further advancements in the treatment of locally advanced, recurrent, or metastatic cervical cancer. Development of the immune checkpoint blockade PD-1 and CTLA-4 inhibitors has shown promise and will need to be further studied as a means to achieve a durable response in cervical cancer.

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Expert Perspective on ASH 2014: Lymphoma

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Abstract

The 2014 Annual Meeting and Exposition of the American Society of Hematology included many updates of previously presented studies, as well as data on different therapeutics and novel targeted agents. This perspective highlights some of the key findings in lymphoma.

Key words: Lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, T cell lymphoma, chronic lymphocytic lymphoma

The latest Annual Meeting and Exposition of the American Society of Hematology (ASH), held from December 6-9, 2014, in San Francisco, included many updates on studies that we had received preliminary data on in the past, as well as additional information on different therapeutics, including interesting data on some of the novel targeted agents. Presented here are some of the lymphoma findings from the conference, arranged by malignancy subtype. (The February issue of *The American Journal of Hematology/Oncology* will feature an update on leukemia abstracts presented at ASH.)

Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is an aggressive form of lymphoma with 2 subtypes—germinal-center B cell (GCB) and non-GCB, or activated B cell (ABC), depending on whether the determination is made by immunohistochemistry or gene expression, respectively.. We already know that lenalidomide has demonstrated activity in DLBCL. A retrospective analysis showed that patients with the non-GCB subtype appeared to have a better response to lenalidomide monotherapy compared with patients with the GCB subtype.[1] Therefore, a prospective, phase 2/3, multicenter, randomized study was initiated to compare the efficacy and safety of lenalidomide as a single agent versus investigator's choice (gemcitabine, rituximab, etoposide, or oxaliplatin monotherapy) in relapsed/refractory DLBCL (study DLC-001).[2]

With 25 patients in each major subgroup (GCB or non-GCB) either receiving lenalidomide or investigator's choice, the most pronounced clinical benefit was observed in patients with the ABC subtype with single-agent lenalidomide. Unfortunately, the lenalidomide activity was just short of what we wanted to see in order to proceed with clinical development, and so this trial did not proceed from phase 2 to phase 3. What this showed, however, was that there is a signal for improvement in the relapsed setting with lenalidomide in the ABC phenotype.[2] Also, perhaps in the future, lenalidomide combined with other agents that are active in relapsed/refractory ABC DLBCL will be evaluated to determine if the combinations will result in improved therapeutic outcomes. In addition, lenalidomide is currently being studied prospectively in combination with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) in several trials in patients with ABC DLBCL in the upfront setting.

Even though CD30 is the target for brentuximab vedotin (SGN-35), past data have shown that the drug may be active in some patients despite undetectable surface CD30 expression (as measured by immunohistochemistry).[3] Preliminary results from a phase 2 trial of brentuximab vedotin monotherapy for patients with DLBCL with undetectable CD30 were also reported. One dose of brentuximab vedotin was administered every 3 weeks until progression or intolerability. Of the 51 patients enrolled, the overall response rate (ORR) was 31%, including 10% of patients who achieved complete response (CR). Unfortunately though, the median duration of response (DOR) was only 1.9 months, and the median progression-free survival (PFS) was only 1.4 months. There were no new toxicity data compared with previous historical results.[4] Despite some activity, as a single agent it is limited based on these data, and so studies are currently being planned in CD30+ DLBCL utilizing brentuximab vedotin with other agents to improve antitumor activity.

In order to determine whether changing the CD20 antibody could benefit patients receiving salvage therapy, a randomized phase 3 study of ofatumumab versus rituximab salvage chemoimmunotherapy in relapsed/refractory DLBCL was performed in Europe. A total of 447 autologous stem cell transplant–eligible patients were randomized: 222 to ofatumumab (O)-DHAP (cisplatin, cytarabine, dexamethasone) and 225 to rituximab (R)-DHAP, in an attempt to improve PFS and outcomes after autologous stem cell transplant. Notably, no difference in efficacy was found between the ofatumumab or rituximab arms when combined with DHAP.[5]

Even though activity was described in these 3 abstracts in relapsed/refractory DLBCL, we still need to find either novel

agents or novel combinations that will help us improve outcomes in this patient population (especially in patients not cured with upfront therapy).

Follicular Lymphoma

Recent data demonstrated significant activity of the combination of lenalidomide plus rituximab in patients with relapsed/refractory or newly diagnosed follicular indolent lymphoma (FL). In a European study in patients with untreated FL who were in need of therapy, 154 patients were randomized to rituximab alone (typical dose and schedule) or to rituximab plus lenalidomide (R^2), which was administered at 15 mg/day for a total of 19 weeks. The ORR in the combination arm was 81% versus just 61% in the rituximab-alone arm. The CR rate in the combination group was 36% compared with only 25% with rituximab monotherapy, which was highly statistically significant.[6] Further follow-up will be needed because it is still early, but these findings support previous data showing that this combination is quite effective in patients with either FL or indolent lymphoma.

Final results were presented from the maintenance part of the phase 1b GAUDI study of upfront/first-line obinutuzumab (GA-101) plus CHOP or bendamustine in FL. Patients were randomized to either G (obinutuzumab)-CHOP (n = 41) or G-bendamustine (n = 40). Patients who responded then received obinutuzumab 1000 mg maintenance therapy (n = 72, 36 in each arm) every 3 months for 2 years or until progression of disease. The CR rates at the end of maintenance compared with after induction appeared to improve somewhat. In addition, at the end of maintenance therapy, the CR rate in patients who received G-bendamustine induction was 60% and the CR rate in patients who received G-CHOP induction was 70%. Most patients were progression-free at 32 months of median follow-up. There were some cases of clinically relevant neutropenia (about 14% of patients who received G-bendamustine).[7] These data have led to a phase 3 study (GALLIUM) being conducted now to further evaluate the difference between rituximab and obinutuzumab when we combine them with chemotherapeutic agents in untreated indolent lymphoma.

Preliminary results of a phase 2 trial in FL of ibrutinib, an oral agent that inhibits Bruton's tyrosine kinase (BTK), were presented at this year's meeting. Forty patients with relapsed/refractory FL received continuous dosing of ibrutinib 560 mg/day in 28-day cycles until progression or intolerability. The ORR was 28%, which included a 5% CR rate, revealing modest activity. The levels of activity seen with ibrutinib have been higher in relapsed/refractory chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL) (for which the drug is already approved by the FDA). An interesting part of the current study, however, is that the response rate was higher (42%) in rituximab-sensitive patients, but the response rate was only 6% in patients who were rituximab-refractory. It appears that these patients with rituximab-refractory disease are more resistant to ibrutinib activity for some reason.[8] Further research will be needed to clarify these results, along with research into combination therapies to determine the optimal utilization of ibrutinib-based therapy for FL.

A phase 1 evaluation of duvelisib (IPI-145), which is an oral PI3 kinase-γ and -δ inhibitor, was conducted in patients with relapsed/refractory indolent lymphoma. Of the 36 patients treated with duvelisib, which was safely dosed at 25 mg twice a day, most had FL. The safety profile was found to be acceptable, with most patients having only grade 1 or 2 toxicity. As is common with the PI3K-δ inhibitor idelalisib, transient increases were seen in the liver enzymes ALT and AST with duvelisib. Neutropenia or pneumonia was seen in about 11%, which were grade 3 or 4 in some patients.[9] A total of 13 of 18 (72%) patients had objective responses. Of these 18, 6 (33%) achieved CR. The median PFS was not reached, but the observation time is still relatively short and so it will have to be monitored further.[9] Additional phase 2 and phase 3 studies evaluating this dose (25 mg twice daily) in patients with indolent lymphoma as monotherapy or in combination with rituximab are currently ongoing.

Mature follow-up data from a phase 2 trial of idelalisib in heavily pretreated patients (median of 4 prior therapies) with double-refractory (to both rituximab and an alkylating agent) indolent lymphoma were presented. A total of 126 patients received oral idelalisib 150 mg twice daily continuously until progression or intolerability. There was a 58% ORR out of 125 patients, with a 56% response in patients with FL and 61% in small lymphocytic lymphoma (SLL); responses were also seen in some of the small numbers of patients with marginal zone lymphoma (MZL) or lymphoplasmacytic lymphoma. The median DOR was found to be 12.5 months. The safety profile was similar to previous reports of idelalisib safety. Phase 3 trials of idelalisib in combination with rituximab or bendamustine plus rituximab are ongoing.[10]

In a small phase 1b study, 20 patients with relapsed or refractory grade 1, 2, or 3a FL were treated with a total of 8 fixed doses of obinutuzumab (GA-101) 1000 mg in combination with lenalidomide in cohorts from 10 to 25 mg for 6 cycles. The maximum tolerated dose (MTD) was not reached. The recommended lenalidomide dose was chosen to be 20 mg because there was more significant neutropenia between cycles 2 and 6 with 25 mg dosing. The combination was well tolerated overall. In the 19 evaluable patients, there was a 63% ORR, which interestingly included about 58% CRs.[11] Currently, studies are assessing the efficacy of the 20-mg dose of lenalidomide plus the obinutuzumab schedule in patients with relapsed/refractory FL and in patients with relapsed/refractory aggressive lymphomas (including those with either DLBCL or MCL).

Mantle Cell Lymphoma

Mature findings were revealed for a phase 2 study that was presented about a year ago of the biological doublet of lenalidomide plus rituximab as initial treatment for MCL. Patients received induction therapy, and those who responded would also continue on the combination until progression of disease. These patients represented typical cases of MCL that were in need of initial therapy. No new toxicity was seen in the 38 treated patients, but patients did experience cytopenias, as is expected with lenalidomide therapy. Patients had evidence of grade 1 or 2 infections that responded to antibiotic therapy. Efficacy results in the intent-to-treat (ITT) population were quite impressive: 84% ORR,

TABLE. Selected Lymphoma Abstracts: ASH 2014

Author/Abstract Number	Comparison	Results Overview
Diffuse Large B-Cell Lymphoma		
Czuczman/628[2]	• R/R disease • Single-agent lenalidomide vs IC • GCB subgroup (n = 50) • Non-GCB/ABC subgroup (n = 50)	• Results suggest some enrichment of clinical benefit (PFS, OS) with single-agent lenalidomide in the non-GCB population; difference appears more pronounced in the ABC population • Data did not meet prespecified criterion to advance to phase 3 trial
Bartlett/629[4]	• Phase 2; pts with undetectable CD30; N = 51 • Brentuximab vedotin every 3 weeks	• ORR 31%, including 10% CR • Median DOR 1.9 months • Median PFS 1.4 months
Van Imhoff/630[5]	• Phase 3; R/R disease, autologous stem cell transplant-eligible pts • Ofatumumab-DHAP: n = 222 • Rituximab-DHAP: n = 225	• No difference in efficacy between the 2 treatment arms
Follicular Lymphoma		
Kimby/799[6]	• R/R or newly diagnosed, untreated disease; N = 154 • Single-agent rituximab vs rituximab plus lenalidomide 15 mg/day for 19 weeks	• ORR: 19% rituximab-lenalidomide vs 61% rituximab only • CR: 36% rituximab-lenalidomide vs 25% rituximab only
Dyer/1743[7]	• Phase 1b maintenance phase; first-line, follicular non-Hodgkin lymphoma • Obinutuzumab-CHOP: n = 41 • Obinutuzumab-bendamustine: n = 40 • Responding pts received obinutuzumab 1000 mg maintenance every 3 months for 2 years or until progression (n = 36 per arm)	At the end of maintenance therapy: • CR: 60% obinutuzumab-bendamustine vs 70% obinutuzumab-CHOP • Clinically-relevant neutropenia: approximately 14% in obinutuzumab-bendamustine group
Bartlett/800[8]	• Phase 2, preliminary results; R/R disease • Ibrutinib 560 mg/day in 28 day cycles • N = 40	• ORR, 28%, including 5% CR • Response rate: 42% in rituximab-sensitive pts vs 6% in rituximab-refractory pts
Flinn/802[9]	• Phase 1, R/R indolent lymphoma • Duvelisib, safely dosed at 25 mg twice daily; n = 36	• ORR: 72%, including 33% CR • Median PFS: not reached • Transient increases in ALT and AST • Neutropenia or pneumonia: 11% (some grade 3 or 4)
Gopal/1708[10]	• Phase 2 double-refractory indolent lymphoma • Idelalisib 150 mg twice daily	• ORR: 58%: 56% in FL; 61% in SLL • Median DOR: 12.5 months
Morschhauser/4458[11]	• Phase 1 b, R/R FL grade 1, 2, or 3a • N = 19 evaluable pts • Obinutuzumab,1000 mg; 8 fixed doses plus lenalidomide • Cohorts from 10 mg to 25 mg for 6 cycles	• MTD: not reached • ORR; 63%, including 58% CR • Recommended lenalidomide dose chosen: 20 mg
Mantle Cell Lymphoma		
Ruan/625[12]	• Phase 2 • Lenalidomide plus rituximab as initial treatment	ITT population: • ORR: 84%, with 55% CR • Median time to PR: 3 months • Median time to CR: 11 months • 2-year PFS: 85%
Trneny/626[13]	• Phase 2; R/R disease • N = 254 • Lenalidomide vs IC • Crossover to lenalidomide allowed on progression	• ORR: 40 % lenalidomide vs 11% IC • Median PFS: 9 months lenalidomide vs 5 months IC • Median DOR: 16 months lenalidomide vs 10 months IC • OS: 28 months lenalidomide vs 21 months IC
Wang/627[14]	• Phase 2; relapsed disease • Ibrutinib and rituximab; after 2 years, ibrutinib alone	• ORR: 68%, 40% CR • Proliferation or Ki-67 index <50% in MCL cells: ORR 100% • Ki-67 index ≥50%: ORR 50%

TABLE. Selected Lymphoma Abstracts: ASH 2014 (continued)

Author/Abstract Number	Comparison	Results Overview
T-Cell Lymphoma		
Dupuis/504[15]	• Phase 1/2 trial; previously untreated PTCL; n = 18 in phase 1b; n =19 in phase 2 • Romidepsin plus CHOP	• ORR: 68%, including 51% CR • Estimated 12-month PFS: 57% • Estimated 12-month OS: 82% • Significant hematologic toxicities, including grade 3 and 4 events: grade 3/4 neutropenia and thrombocytopenia
Chronic Lymphocytic Leukemia		
Zelenetz/1986[16]	• Phase 2, previously untreated pts age ≥65 years with either CLL or SLL • Idelalisib monotherapy	• ORR: 87%, consisting of 47% PR and 40% PR + lymphocytosis rate
O'Brien/327[17]	• Phase 2, open label, RESONATE™-17 trial; pts with R/R CLL/SLL with 17p deletion • Ibrutinib 420 mg orally once daily	• ORR: 83% • 12-month PFS (median not yet reached): 80%
Sharman/330[19]	• Phase 3; relapsed CLL with 17p deletions and other adverse prognostic factors • Idelalisib plus rituximab vs placebo plus rituximab	• PFS strongly favored idelalisib plus rituximab in all risk subgroups, including genetic risk factors (eg, 17p deletion), as well as disease-related risk factors (eg, Rai stage)
Kovacs/23[20]	• Combined analysis of two phase 3 trials in CLL • FC vs FCR; and FCR vs bendamustine + rituximab (545 pts with MRD)	• MRD plus clinical response predicted PFS more accurately than clinical response alone
Novel Therapies		
Lunning/801[21]	• Heavily pre-treated CLL and B-cell lymphoma • Ublituximab plus TGR-1202	• CLL: ORR, approximately 67% • DLBCL: ORR, 43% (3 of 7 pts), 2 pts with CR
Armand/289[22]	• R/R Hodgkin lymphoma • Nivolumab • N = 23	• ORR: 87% (20 of 23 pts), including 17% CR • 6-month PFS: 86% • Decrease in platelet counts: 20% • Diarrhea, nausea, fatigue or fever: >10%
Lesokhin/291[23]	• Phase 1 preliminary results • Various R/R disease, including FL or DLBCL, and T-cell lymphomas • Nivolumab	• DLBCL: 36% (4 of 11 pts) achieved a response • FL: 40% (4 of 10 pts) achieved a response • Mycosis fungoides: 15% achieved a response (2 of 5 pts) • Multiple myeloma: 0% response (0 of 27 pts)
Moskowitz/290[24]	• Phase 1b • Classical Hodgkin lymphoma after brentuximab vedotin failure • Pembrolizumab every 2 weeks for 6 cycles • N = 15	• ORR: 53% • CR: 20% • PR: 33%

ABC indicates activated B cell; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CLL, chronic lymphocytic leukemia; CR, complete response; DHAP, cisplatin, cytarabine, dexamethasone; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; FL, follicular lymphoma; GCB, germinal-center B cell; IC, investigator's choice; ITT, intent to treat; MCL, mantle cell lymphoma; MRD, minimal residual disease; MTD, maximum tolerated dose; OS, overall survival; ORR, overall response rate; PR, partial response; pts, patients; PFS, progression-free survival; R/R, relapsed refractory; SLL, small lymphocytic lymphoma.

with 55% of patients achieving CR. Of the 36 evaluable patients, the ORR was 89%, with a 58% CR rate. Notably, the 2-year PFS was 85%.[12] This was the first study to show activity and the feasibility of the combination of lenalidomide and rituximab as frontline therapy for MCL. Patients with higher MCL International Prognostic Index (MIPI) scores or proliferation (or Ki-67) indices typically have lower response rates with other therapies. Interestingly, in this study, patients with poor prognostic scores had similar response rates to those of patients with better prognostic features. These data justify further evaluation of this combination, either by itself or maybe with the integration of other novel agents active in the treatment of patients with MCL.[12]

A phase 2, randomized, multicenter study (MCL-002) of lenalidomide versus best investigator's choice in relapsed/refractory MCL was conducted in 254 patients. Patients received either single-agent lenalidomide 25 mg/day on days 1 through 21 every 28 days until progression or toxicity, or investigator's choice (eg, cytarabine, rituximab, gemcitabine, fludarabine, or chlorambucil). Patients who progressed on one of these agents were allowed to cross over to receive lenalidomide. The ORR with lenalidomide was 40% compared with only 11% with investigator's choice, and median PFS was 9 months to approximately 5 months, re-

spectively. The median DOR was improved with lenalidomide: 16 months versus 10 months (with investigator's choice). There was some improvement in overall survival (OS), with 28 versus 21 months, keeping in mind some patients did cross over, which could confound these results. Since single-agent lenalidomide has already been FDA-approved for the treatment of patients with relapsed/refractory MCL, this is additional data demonstrating definite antitumor activity in this patient population, marking its superiority over standard single-agent chemotherapy alone.[13]

Preliminary results from a phase 2 trial of the combination of ibrutinib and rituximab in patients with relapsed MCL were presented. Patients received ibrutinib 560 mg/day until progression or intolerability combined with rituximab 375 mg/m^2 weekly × 4 (cycle 1) and then 1 dose per cycle (cycles 3 through 8), and then 1 dose every other cycle for up to 2 years. After 2 years, ibrutinib was given as a single agent until progressive disease or intolerance. Definite efficacy of the combination was shown, with a 68% ORR and 40% of patients achieving CR. It was interesting that patients with a proliferation (or Ki-67) index <50% in MCL cells benefited the most, with 34/34 (100%) patients responding. In patients with ≥50% Ki-67, ORR was only 50%. There were also more CRs in patients with lower Ki-67 scores. Therefore, Ki-67 could become a potential biological marker that could help inform us which patients may benefit most from this treatment combination.[14]

T-Cell Lymphoma

One of the more interesting lymphoma studies presented at ASH was of a histone deacetylase (HDAC) inhibitor called romidepsin in combination with CHOP in patients with previously untreated peripheral T-cell lymphoma (PTCL). These are the final results of the phase 1/2 trial. A total of 18 patients were included in the phase 1b trial, with 19 in phase 2. Different dosing cohorts of romidepsin were evaluated with standard CHOP. There was an ORR of 68% (24/35 evaluable patients), including a 51% CR rate. The estimated 12-month PFS was about 57%, and the estimated 12-month OS rate was 82%. Although this study demonstrated that romidepsin can be combined with CHOP, there were also significant hematologic toxicities reported (including grade 3 and 4 events). The majority of patients experienced grade 3/4 neutropenia, and over one-third of the patients had grade 3/4 thrombocytopenia. A significant amount of growth factor was utilized for these patients. But considering that this population is often treated with standard CHOP therapy, the PFS improvement at least seems promising with this combination.[15] A phase 3 study is now comparing CHOP alone versus the combination of romidepsin-CHOP.

Chronic Lymphocytic Leukemia

One abstract from ASH reported a phase 2 trial of idelalisib monotherapy, a PI3K-δ inhibitor, in previously untreated patients ≥65 years with either CLL or SLL. Idelalisib has been approved for use in the relapsed setting, but this study is interesting because it shows definite activity in previously untreated patients. There was an 87% ORR rate in these treatment-naïve older patients, consisting of a 47% partial response (PR) rate and a 40% PR + lymphocytosis rate (ie, patients with evidence of lymphocytes circulating in the blood who still had a ≥50% shrinkage of their adenopathy). As expected of single-agent idelalisib, peripheral lymphocytosis was increased early after initiating therapy. The safety profile was similar to that seen with prior trials, and toxicity was tolerable.[16]

The open-label, phase 2 RESONATE™-17 trial investigated the safety and efficacy of ibrutinib in patients with relapsed/refractory CLL/SLL with 17p deletion. This was the largest prospective trial in this subpopulation, including 144 patients who had received 1 to 4 prior lines of therapy. Oral ibrutinib was given at the typical dosage of 420 mg orally once daily until either unacceptable toxicity or disease progression. The ORR was 83%. The median PFS and DOR were not reached from the short follow-up, but at 12 months, PFS was around 80%.[17] This PFS was similar to the PFS seen in patients treated with fludarabine, cyclophosphamide, and rituximab (FCR) as combination upfront therapy in CLL.[18] It should be noted that ibrutinib is also FDA-approved for patients with 17p deletion in the setting of newly diagnosed, previously untreated CLL.

A second interim analysis of a phase 3 study of idelalisib plus rituximab in relapsed CLL was available, showing efficacy analyses in patients with 17p deletions and other adverse prognostic factors. This trial demonstrated that idelalisib has significant activity in this population. Patients in this trial had similar efficacy with idelalisib plus rituximab in the presence or absence of high-risk genomic abnormalities. Patients with, for example, a 17p deletion, achieved similar results as those with better prognostic factors, without new toxicity.[19]

One of the most important things about CLL to take home from this ASH meeting was that there appears to be potential value in measuring minimal residual disease (MRD) status as a CLL response evaluation. A combined analysis of 2 large phase 3 trials (CLL-8 and CLL-10) of the German CLL Study Group looked at patients who had received fludarabine and cyclophosphamide (FC) versus FCR in one study or FCR treatment versus bendamustine and rituximab in the other. There were almost 1400 patients at the outset, with 545 patients with MRD analysis. MRD and clinical response were both strong predictors, but the best combination was getting MRD in combination with clinical response, which predicted PFS more accurately than just looking at clinical response. In other words, evaluating just CR or PR was not as meaningful as achieving a MRD state was (eg, MRD-negative CRs achieved a larger PFS than MRD-positive CRs).[20]

It was also interesting that splenomegaly as the sole abnormality at the end of the treatment response did not impact PFS in patients who were MRD-negative. In other words, these patients still had splenomegaly and were considered to have a clinical PR, but as long as the blood was completely cleared down to MRD, those patients actually did as well as patients who had achieved a clinical CR. The patients that will fare the best are ones who have both a decrease in the nodal disease and a clearing of the blood of these abnormal CD19+, CD5+, CD23+ cells (the typical phenotype of CLL). We may be seeing more of this

evaluation in the future, possibly included as part of prospective trials, as not just the achievement of a clinical CR, but more so the "quality" of the CR (ie, MRD status) may actually be a very important end point in future CLL clinical trials.[20]

Novel Lymphoma Therapies

A new CD20 antibody, ublituximab, was combined with a novel, next-generation PI3K-δ inhibitor, TGR-1202 in heavily pretreated and high-risk CLL and B-cell lymphoma. Ublituximab, a second-generation monoclonal antibody, binds to a unique CD20 epitope compared with the other CD20 antibodies, such as rituximab or ofatumumab. It is interesting that the PI3K-δ inhibitor, TGR-1202, is administered only once a day (800 mg), whereas patients treated with idelalisib typically receive it twice daily. Also of note is that there was no significant increase in liver enzymes with this combination, which is usually expected with PI3K-δ inhibition using idelalisib. It could be that this is secondary to its unique molecular structure; it will be interesting to see future updates. In CLL, the ORR was about 67%. The patient numbers were small; for example, in DLBCL there was a 43% ORR, but that was in only 3 out of 7 patients. But still, there appears to be a preliminary positive signal of activity, including 2 patients with DLBCL who achieved CR. There has been no liver toxicity to date in 87 patients treated with the PI3K-δ inhibitor.[21]

A tremendous amount of excitement has been generated by the so-called immune checkpoint inhibitors–in particular, inhibitors of the programmed death 1 (PD-1) receptor or programmed death ligand 1 (PD-L1). Many tumors actually have these ligands, and once the ligand binds to the PD-1 receptor on T cells, the activity of the T cell is downregulated. Therefore, if we can block the interaction between the PD-1 receptor and the PD-L1 ligand, the innate immune system will remain intact.

The PD-1 inhibitor nivolumab, which is a human IgG4 monoclonal antibody that blocks PD-1, has been studied in patients with relapsed/refractory Hodgkin lymphoma. Out of 23 patients, 20 responded, so the ORR was 87%, including a 17% CR rate and a 6-month PFS rate of 86%, which are remarkable numbers. There was some toxicity, the most common being rash, some decrease (20%) in platelet counts, and >10% of patients with either diarrhea, nausea, fatigue, or fever. But, in general, the agent was very well tolerated. These results are quite incredible in this heavily pretreated patient population, and it is amazing to have this kind of a single-agent response rate simply by bestowing the ability to allow the immune system to do its job. Based on these important results, the FDA granted nivolumab breakthrough status in relapsed classical Hodgkin lymphoma, and there is a large, multinational phase 2 trial of this therapy currently under way.[22]

In addition to Hodgkin lymphoma, preliminary results of a phase 1 study of nivolumab were also described in various relapsed/refractory lymphoid malignancies, including B-cell lymphomas, either FL or DLBCL, or T-cell lymphomas–such as mycosis fungoides or PTCL–as well as a number of patients with multiple myeloma. Of the evaluable patients, 4 out of 11 (36%) patients with DLBCL achieved a response. Out of the 10 patients with FL, responses were seen in 4 (40%). Roughly 15% of patients with mycosis fungoides and 40% with PTCL responded. It should be noted that 0 out of the 27 patients with multiple myeloma had an objective response to treatment with this novel agent. Additional multicenter, phase 2 trials are ongoing, in particular in DLBCL and FL.[23]

Another anti-PD-1 monoclonal antibody called pembrolizumab was studied in a phase 1b trial in patients with classical Hodgkin lymphoma after brentuximab vedotin failure. Patients (N = 15) received pembrolizumab every 2 weeks for 6 cycles of treatment. Re-staging was demonstrated at week 12 with a 53% ORR, 20% CRs, and 33% PRs. Again, it is very exciting that, by not allowing the PD-L1 ligand to bind to the PD-1 receptor and suppress T cell activity, we can allow the T cells to do the job that they were born to do.[24]

Conclusion

At ASH, we were exposed to updated data for existing treatments and exciting data with investigational combinations utilized to treat various lymphoid neoplasms. In addition, new data were revealed on some of the novel targeted agents, in particular checkpoint inhibitors, which harness the potential of not blocking the body's immune system to fight cancer, a strategy which has demonstrated very exciting preliminary results in hematologic malignancies, as well as recently in solid tumors.

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Recently, several melanoma experts convened in Dallas to discuss clinical issues important to community oncologists when treating patients with melanoma. They were Jeffrey Weber, MD, PhD, senior member and director of the Donald A. Adam Comprehensive Melanoma Research Center at Moffitt Cancer Center in Tampa, Florida; Adil Daud, MD, professor in the Department of Medicine at the University of California, San Francisco Medical Center, and also at the Helen Diller Comprehensive Cancer Center in San Francisco; Ragini Kudchadkar, MD, assistant professor at Winship Cancer Institute of Emory University School of Medicine in Atlanta, Georgia; and Mario Sznol, MD, professor of Medicine at Yale School of Medicine and co-director of SPORE in Skin Cancer at Yale Cancer Center in New Haven, Connecticut.

During their discussion, these experts focused on some of the most common clinical challenges associated with treating patients with metastatic melanoma. Patients with metastatic melanoma used to have few treatment options, but in the past several years, 5 new agents have been introduced into the care of these patients, including new immunotherapies, BRAF inhibitors, and a MEK inhibitor. Although these therapies have provided much-needed treatment options, their existence has also created a number of practical challenges that directly impact patient management, including who should receive these agents, how to sequence them, if they should be provided in combination with one another, and how to manage their associated toxicities. The following is a discussion of these and other relevant melanoma topics by Drs Weber, Daud, Kudchadkar, and Sznol.

Treatment of Patients With Brain Metastases

Dr Weber: We'll begin our time today by discussing the treatment of brain metastases in patients with melanoma. These patients represent one of the most challenging populations of melanoma patients, due to the inability of most conventional agents to cross the blood-brain barrier. Ragi, which of the new agents are being utilized in this difficult-to-treat population?

Dr Kudchadkar: When we see patients with brain metastases, it creates new challenges for us, both in how to utilize standard therapies, like surgery and radiation, and systemic therapies. It's very clear that the BRAF inhibitors, both vemurafenib and dabrafenib as well as dabrafenib/trametinib combination therapy, have activity in the brain. Ipilimumab has also established responses in the brain. There are fewer data on the response rates in the central nervous system of the PD-1 antibodies nivolumab and pembrolizumab.

The response rates in general for systemic therapies in the brain are approximately 20% to 30%, depending on how you measure response. Patients with brain metastases are always challenging because they are often receiving steroid therapy, which contraindicates the use of immunotherapies like ipilimumab and nivolumab. However, I think other systemic therapies are great options for patients with brain metastases who have high systemic disease burden outside the brain. This is especially true when the brain metastases are so small—in the millimeter range—as is becoming common with surveillance MRIs.

Dr Weber: Are there circumstances in which you would dispense with radiation and simply treat a patient with brain metastases by using systemic therapy alone?

Dr Kudchadkar: I think the role of whole-brain radiation is rapidly diminishing because its toxicities have become more evident as our patients live longer. I think patients with a high burden of systemic disease and a very low burden in the brain can be considered for systemic therapy alone. Also, utilizing stereotactic radiation and surgery for solitary or symptomatic brain metastases rather than whole-brain radiation allows us to use more systemic therapy earlier in the course of these patients.

Dr Weber: Adil, are there scenarios in which you've had success using ipilimumab in patients with brain metastases?

Dr Daud: We've had some patients with amazing responses to ipilimumab. I have 1 patient with multiple brain metastases who was treated with ipilimumab 3 years ago. She subsequently developed hypophysitis and has been on chronic steroid replacement therapy, but she's still free of disease both systemically and in the brain. However, I wouldn't say response rates are higher in the brain. I think responses to systemic agents are in the 10% to 30% range, and these rates tend to be lower in the brain.

Dr Weber: Mario, have you treated patients who have brain metastases with BRAF or BRAF/MEK inhibitors and achieved long-term survival?

Dr Sznol: No, but that's not because it can't occur. We're very aggressive treating metastatic disease in the brain upfront with Gamma Knife radiation. We have not yet tried to treat these patients with targeted agents or immunotherapy alone. However, one exception is an ongoing clinical trial of pembrolizumab in patients with active brain metastases.

Dr Daud: I also can't say that with targeted agents alone I've seen long-term responses in patients with multiple brain metastases—not without using stereotactic radiation as well.

Dr Kudchadkar: I've had patients on trials who have had responses in the brain, but they haven't been long term. We use systemic agents primarily to reduce disease burden and get patients off steroid therapy, which opens more options for systemic therapy.

Dr Weber: I've had the best experience with patients who receive either ipilimumab or PD-1 antibodies, but I always radiate the disease first and then administer the immunotherapy because I believe that destroying the local tumor might produce immunologic priming. There is evidence of this in the pivotal ipilimumab 020 trial. In that trial, the 11% of patients who had previously radiated brain metastases had outcomes as good as those without brain metastases, suggesting that simply by radiating the brain metastases, the immune system is somehow primed to more successfully control the disease in the brain.

Dr Sznol: In the absence of a clinical trial, I do things differently, starting with ipilimumab, and then later giving the stereotactic radiation. When giving stereotactic radiation first, I worry about a couple of things: patients receiving Gamma Knife radiation can develop late radiation necrosis, which is very difficult to differentiate from metastatic disease. In addition, some patients can develop substantial neurologic complications from the vasogenic edema related to radiation necrosis. We have surgically removed very large lesions that have turned out to be purely ra-

diation necrosis. We have also started seeing MRI reports of new metastatic lesions in the brains of patients treated 2 years earlier with Gamma Knife radiation. These lesions are often just areas of recurrent enhancement and radiation necrosis in the previously treated area. When following them over time, sometimes that enhancement disappears without any additional treatment.

The other phenomenon we've seen is in patients previously treated with immunotherapy who develop new brain metastases. If they don't have significant edema and the lesions are small, we sometimes simply follow the disease, particularly if they had responded systemically to the immunotherapy. In these patients, just like with pseudo-progression in the body, we sometimes see those lesions disappear.

Dr Kudchadkar: We have had a very similar experience at Emory with development of radiation necrosis 6 months or a year after systemic therapy. We recently had a patient who we thought had developed tumor progression more than 1 year after radiation therapy, but after surgically removing the tumor, we found it was only radiation necrosis.

Dr Sznol: I think it is very important to emphasize that radiation necrosis may not develop all at the same time. Lesions can start to show more vasogenic edema or appear to progress months apart from one another.

Using Combination Therapy for Patients With *BRAF*-Mutated Metastatic Melanoma

Dr Weber: Let's move on to our next topic, which is combination therapy for patients with *BRAF*-mutated disease. This topic is of great interest, thanks to the recent ESMO meeting in which 3 pivotal trials testing 2 different combination regimens were presented (**Table 1**). Results from one of these trials, COMBI-d, has already been published in *The New England Journal of Medicine*.[1] In the COMBI-d study, patients were randomly allocated to receive either dabrafenib plus trametinib, the BRAF/MEK inhibition combination, or dabrafenib alone, which is now approved as monotherapy for metastatic disease. Results of this large phase 3 study showed that progression-free survival (PFS), the primary end point, was clearly greater for the combination than for the single-agent dabrafenib. The difference in median PFS was pretty modest (9.3 months vs 8.8 months), but the PFS hazard ratio was 0.75, and response rate was also superior for the combination therapy (67% vs 51%). Because this was a crossover study, the overall survival (OS) data were modest but significant, with a hazard ratio of 0.63 (P =.02). Not surprisingly, the squamous cell cancer incidence was reduced from 9% with dabrafenib alone to 2% with the combination. In contrast, the incidence of severe fevers was increased, from 2% with monotherapy to 6% with the combination therapy. Overall, the investigators concluded that the toxicity of both arms was a wash, and I think we all agree that COMBI-d was a successful study.

Another study presented at ESMO 2014 was the COMBI-v study. In this large randomized study, 704 patients were randomly allocated to either dabrafenib/trametinib or the then-standard single-agent vemurafenib. The primary end point was OS, with a planned interim analysis after half of the death events occurred. This study was stopped at the time of interim analysis because of its clearly positive results. Response rate was significantly better for the combination regimen (64% vs 51%; P <.001), and the OS hazard ratio of 0.69 favored the combination arm (P =.005), stopping the study because the P value crossed the predetermined boundary.[2] Median survival for the vemurafenib arm was a pretty favorable 17.2 months; median survival of the combination arm has not yet been reached, but back-of-the-napkin calculations suggest that it will be approximately 2 years, which is consistent with survival for dabrafenib/trametinib in phase 2 studies. Median PFS for the combination was 11.4 months compared with 7.3 months for vemurafenib alone, with a hazard ratio of 0.56 (P <.001).

Finally, the last ESMO 2014 trial was coBRIM, another large, definitive, randomized melanoma study. This time, vemurafenib was combined with a novel MEK inhibitor, cobimetinib, and compared with vemurafenib alone. The primary end point was PFS, and the investigators projected that the addition of cobimetinib would improve median PFS from 6 months to 11 months.

TABLE 1. Primary Outcomes of Three Phase 3 Combination Trials in Metastatic Melanoma[1-3]

Study Name/ Trial Number	Study Design	Primary Outcome	HR	*P* Value
COMBI-d/ NCT01584648	Dabrafenib/trametinib vs dabrafenib	PFS: median, 9.3 vs 8.8 months	0.75	.03
COMBI-v/ NCT01597908	Dabrafenib/trametinib vs vemurafenib	OS: median, NR vs 17.2 months	0.69	.005
coBRIM/ NCT01689519	Vemurafenib + cobimetinib vs vemurafenib	PFS: median, 6.0 vs 11.3 months	0.60	.0003

HR indicates hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.

In this trial, as with the other combination trials, combination therapy reduced the skin toxicity seen with vemurafenib alone but other toxicities showed an increase, primarily cardiac issues and serous retinopathy.[3] The difference in response rate was striking, with 68% for the combination regimen versus 45% for vemurafenib. Just as investigators predicted, median PFS improved from exactly 6 months with single-agent vemurafenib to 11.3 months for vemurafenib/cobimetinib. The hazard ratio was 0.60 (P =.0003). Despite the crossover design of this study and its relatively short follow-up, there was a significant difference in OS, with a hazard ratio of 0.65 (P =.046).

Adil, do you think the data from these 3 combination trials will have a major impact on clinical practice in the community?

Dr Daud: Yes, I do. I personally have difficulty coming up with a patient to whom I wouldn't give combination therapy. Perhaps someone who has congestive heart failure or a history of glaucoma, but I don't think I've treated anyone with a BRAF inhibitor alone in the last couple of years.

Dr Weber: So, Ragi, how are you going to choose between dabrafenib/trametinib and vemurafenib/cobimetinib when the seemingly inevitable approval for that latter combination comes through?

Dr Kudchadkar: That's going to be a difficult choice, but I think it will be decided on toxicity profile. Dabrafenib/trametinib produces more fevers, which can be difficult for patients because they get shaking chills and feel terrible. However, vemurafenib/cobimetinib appears to cause more photosensitivity reactions, so it's a trade-off.

Another reason to choose one combination over the other is reimbursement, but any such differences between the combinations will not be apparent for some time.

Another issue that came up in one of my patients was the importance of pill size. Vemurafenib is given as 4 large pills, which are challenging to swallow. One of my patients had a Zenker's diverticulum, making it difficult to swallow pills, so dabrafenib/trametinib was a better choice for him because he could swallow the smaller pills.

Managing Toxicities of Targeted and Immune Therapies

Dr Weber: Let's turn our attention to our last topic, managing the toxicities associated with these novel agents. Mario, what are some of the most common toxicities associated with the new immunotherapies, like ipilimumab and pembrolizumab, and how do you manage them?

Dr Sznol: Clinicians have extensive experience with ipilimumab, whose primary toxicities are autoimmune-related, specifically rash, colitis or enteritis, elevations of liver function tests, and endocrinopathies that include hypophysitis, thyroiditis, or adrenalitis (**Table 2**). The most dangerous of these is colitis because if it is not controlled, patients can get very sick, develop a bowel perforation, lose their bowel, or even die as a result. The hypophysitis is probably the next most difficult toxicity to manage. Patients present feeling tired, a little confused, possibly with a frontal headache. Often, you can make the diagnosis over the phone because the symptoms are so characteristic. To manage this, you need to draw the right hormone blood studies and start them on low-dose prednisone, and possibly also on thyroid hormones. For colitis, hepatitis, and sometimes rash, steroids are the primary mode of treatment, but for patients resistant to steroids, second-line immune-suppressive agents like infliximab can be used. With all of these toxicities, there are standard algorithms in place for their management, and once you become accustomed to them, they're fairly straightforward to manage.

Dr Weber: Mario, you have a lot of experience at your institution with combination checkpoint protein inhibition, particularly nivolumab and ipilimumab. Do you find that these toxicities are more difficult to manage? Is it a different spectrum?

Dr Sznol: It's not a different spectrum, but the toxicities are definitely more frequent and some are more resistant to steroids, forcing the use of either higher doses of steroids or second-line immune-suppressive agents. Clinicians really need to keep on top of toxicities when you use this combination. For instance, patients who initially respond to steroids may become refractory very quickly. Also, some patients will develop multiple autoimmune toxicities, sometimes across multiple organ systems. However, again, with close monitoring of these patients and good communication between the patient and your staff, these toxicities can be managed very easily in the vast majority of patients. One other point about this combination is that many of the grade 3/4 adverse events are laboratory abnormalities, such as lipase, amylase, and hepatic function elevations. The significance of lipase and amylase elevations is unclear. Obviously, liver function test abnormalities have to be managed with steroids or, in some cases, mycophenolate.

Dr Weber: What kinds of toxicities do you see with targeted agents like the BRAF or MEK inhibitors? Which toxicities are most common, and how do you manage them?

Dr Sznol: Well, the one that we most frequently deal with are the fevers related to dabrafenib and trametinib. It's important not to underestimate the potential severity of these fevers. Some

TABLE 2. Immune-Related Adverse Events Reported in the Ipilimumab-Alone Arm of the Phase 3 MDX-010-020 Trial[4]

Immune-Related AEs	Study Design	
	Total AEs n (%)	Grade 3/4 AEs n (%)
Any immune-related event	80 (61.1%)	19 (14.5%)
Dermatologic	57 (43.5%)	2 (1.5%)
Pruritus	32 (24.4%)	0
Rash	25 (19.1%)	1 (0.8%)
Vitiligo	3 (2.3%)	0
Gastrointestinal	38 (29.0%)	10 (7.6%)
Diarrhea	36 (27.5%)	6 (4.6%)
Colitis	10 (7.6%)	7 (5.3%)
Endocrine	10 (7.6%)	5 (3.8%)
Hypothyroidism	2 (1.5%)	0
Hypopituitarism	3 (2.3%)	2 (1.5%)
Hypophysitis	2 (1.5%)	2 (1.5%)
Adrenal insufficiency	2 (1.5%)	0
Increase in serum thyrotropin level	1 (0.8%)	0
Decrease in serum corticotropin level	2 (1.5%)	1 (0.8%)
Hepatic	5 (3.8%)	0
Increase in alanine aminotransferase	2 (1.5%)	0
Increase in aspartate aminotransferase	1 (0.8%)	0
Hepatitis	1 (0.8%)	0
Other	6 (4.6%)	3 (2.3%)

AE indicates adverse event.

patients feel very sick, and occasionally a patient will get admitted to the hospital with hypotension. We always try to rule out infection. Sometimes fevers "burn out" when treatment is repeatedly stopped and restarted. The other toxicities seem to be easy to manage in these patients.

Dr Daud: Fevers are incredibly common, with over 60% of patients on combination therapy developing some type of fever. However, stopping and restarting dabrafenib/trametinib is an effective way to manage fevers in our hands. Patients should hold both drugs the first time they get a fever and not restart until 24 hours after the fever has subsided. The most common mistake is that patients don't stop treatment and instead add agents like acetaminophen or ibuprofen. In that case, patients can develop very resistant fevers that persist for days or even weeks. However, if they stop and restart treatment, most patients won't have more than a couple of episodes of fevers, and very few will have 4 or more episodes.

Dr Weber: Ragi, do you usually use methylprednisolone to manage fever, or do you just hold the drugs?

Dr Kudchadkar: We usually hold the drugs. The first time someone has a fever, we always do a basic infectious workup, including chest x-ray, urinalysis, and other basic tests, just to make sure we're not missing anything. It's important to note that dose reductions are not effective at managing fevers. Both drugs should be held 3 to 5 days, and then restarted at full doses once fever resolves. Some patients will periodically get fevers every few weeks. I have patients who can feel a fever coming on, and they will simply hold the drugs and have a treatment holiday. For the small group of patients with refractory, persistent fevers, very-low-dose steroids, such as prednisone 10 mg/day or even 10 mg every other day, can provide effective management.

Dr Weber: Mario, what are the side effects you worry most about, aside from the fevers?

Dr Sznol: Aside from fevers, we haven't seen terrible adverse events. There are arthralgias. The squamous cell carcinomas with single-agent therapy are not major problems; we simply surgically remove them. Single-agent dabrafenib, trametinib, or vemurafenib can result in an increase in secondary cancers because of the paradoxical activation of CRAF kinase. However, with combination therapy, I'm not certain there is a corresponding increase.

Dr Weber: In all of the combination studies presented at ESMO 2014, the noncutaneous secondary malignancy rates were equal between arms. However, the head-and-neck cancers, colon cancers—although rare—still scare me because they can be devastating. Mario, what worries you most about managing immunotherapeutic toxicities?

Dr Sznol: Severe colitis and enteritis are probably the most difficult to manage. If you use these agents frequently enough, you will see a whole spectrum of autoimmune toxicities that go beyond rash, colitis, endocrinopathies, and hepatitis. We've seen ascending paralysis, which we managed with IVIg [intravenously administered immunoglobulin] and steroids, severe pneumonitis, hematologic toxicities, and even severe arthralgias requiring

steroid therapy. Those toxicities are rare, but you need to be cautious because adverse events can occur in almost any organ.

Dr Weber: I'd absolutely agree with you. The colitis scares me the most, followed by the neurologic toxicities. The pneumonitis, thankfully, is rare, as are the neurologic and kidney toxicities. The main message, however, is that the vast majority of patients on drugs like pembrolizumab or nivolumab go through treatment with a pretty modest if not minimal level of side effects.

In closing, I'd like to thank each of the panel members for sharing your expertise with us today. Perhaps we can get a clinical pearl from each of you, something that the community oncologist can use right away in caring for their patients with melanoma.

Dr Daud: I would suggest that community oncologists familiarize themselves with either the dabrafenib/trametinib or vemurafenib/cobimetinib combination. That can then be used as a go-to regimen because the data look so similar for each of these combinations.

Dr Kudchadkar: I'd like to emphasize the importance of having specialists lined up who are interested in and familiar with these drugs. These include a dermatologist for skin-related toxicities and squamous cell carcinoma, an endocrine doctor for pituitary and endocrine disorders, and even a neurologist for some of the rarer toxicities. Having a plan for these patients upfront, especially when you're not in an academic environment with specialists down the hall from you, can be helpful in managing any toxicities that develop.

Dr Sznol: I'd like to remind community oncologists to consider clinical trials for their melanoma patients. Some patients obviously can't be referred for clinical trials because of their comorbidities, performance status, or geographic location. However, clinical trials are still crucial to the future advancement of melanoma therapies. We've made so many improvements, but we haven't hit 100% cure rates yet. Some of the new investigational agents may get us closer to that goal. Therefore, in addition to managing patients with the currently available drugs, I would strongly recommend considering a clinical study for those patients who are eligible.

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2. Wierda WG, O'Brien S. Chronic lymphoblastic leukemia. In: DeVita VT Jr, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology,* 9th ed**.** Philadelphia: Lippincott Williams & Wilkins; 2011.
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References

1. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication. [Updated April 2010.] http://www.icmje.org/urm_full.pdf. Accessed October 5, 2012.
2. Iverson C, ed. Ethical and legal considerations. In: *American Medical Association Manual of Style.* 10th ed. New York, NY: Oxford University Press; 2007:125-300.

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