



## New Anticoagulation Therapies in Patients with Cancer

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It is well known that patients with an active malignancy are at increased risk for thrombosis, particularly venous thromboembolism (VTE).<sup>1</sup> VTE affects 4%–20% of patients with cancer and, when all risks from cancer and its treatment are combined, cancer patients have an estimated yearly VTE risk of approximately 1 in 200.<sup>1,2</sup> Patient-specific risk depends on other contributing factors such as age, history of VTE, immobility, type and intensity of chemotherapy regimen, use of antiangiogenic drugs, hormonal therapy, performance status, and primary site and stage of cancer.<sup>3,4</sup> Furthermore, patients with multiple myeloma or who are receiving lenalidomide or thalidomide are at an even higher risk for VTE than patients with other cancers or those who are receiving other therapies. Primary prophylaxis has been shown to decrease the incidence of VTE but is often underutilized in patients with cancer, perhaps owing to unique features in oncology patients that make VTE prophylaxis challenging.<sup>2</sup> Ongoing thrombotic stimulus related to procoagulants from tumors, venous stasis, and endothelial damage from drugs and catheters make VTE prophylaxis complex, and anticoagulant control and monitoring is further

complicated by the need for urgent procedures, variable nutritional intake, intermittent antimicrobial usage, and thrombocytopenia.<sup>5,6</sup>

### VTE Prevention

Controversy exists surrounding the proper patient selection for VTE prophylaxis. The American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines recommend that all hospitalized patients with cancer should be considered candidates for VTE prophylaxis in the absence of bleeding or other contraindication to anticoagulation.<sup>2,3</sup> Prophylaxis is also indicated for patients who have undergone surgery for cancer (extended for up to 5 weeks).<sup>2,3,7,8</sup> However, with the exception of multiple myeloma patients receiving lenalidomide or thalidomide combinations, routine prophylaxis is not currently recommended for ambulatory patients receiving chemotherapy in the outpatient setting.

### VTE Treatment

When VTE does occur, there are still questions remaining about what the best treatment may be. Patients with cancer are at high risk for recurrent

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VTE and bleeding due to malnutrition, liver dysfunction, and nausea and vomiting, which limit the effectiveness of the standard long-term treatment with an oral vitamin K antagonist (VKA). The CLOT trial sought to determine whether the low-molecular-weight heparin (LMWH), dalteparin, would be a more effective long-term therapy option in cancer patients because of its more predictable pharmacokinetic profile and decreased drug-drug interactions.<sup>9</sup> Results from CLOT showed that the risk for symptomatic, recurrent VTE at 6 months was 17% in the oral-anticoagulant group compared with 9% in the dalteparin group, but there was not a significant difference in the mortality rate at 6 months between the two groups, which may lessen the clinical significance of the findings.<sup>9</sup> In addition, LMWHs are expensive and many patients are not comfortable with giving themselves daily injections.

### Impact on Survival

It has been theorized that a direct antitumor effect of heparin may lead to a potential survival benefit in patients with cancer without VTE through the inhibition of cell-cell interaction by blocking cell-adhesion molecules, the inhibition of extracellular-matrix protease heparanase, and the inhibition of angiogenesis.<sup>4,10</sup> Several clinical trials have been conducted to directly study the impact of anticoagulant therapy on overall survival in cancer patients without VTE.<sup>11</sup> A study of 385 patients with advanced malignancy who received dalteparin or placebo for 1 year failed to demonstrate a benefit in survival up to 3 years.<sup>12</sup> However, a post-hoc analysis of 102 patients still alive at 17 months showed significant improvement in survival in patients receiving dalteparin. Another LMWH trial of 302 patients with locally advanced or metastatic solid tumors who received nadroparin or placebo for 6 weeks showed a significant improvement in survival among patients who received nadroparin with a mean follow-up period of 1 year.<sup>13</sup> However, these results were not confirmed by the follow-up study conducted by Sideras and colleagues that randomly assigned 144 advanced solid tumor patients to receive standard treatment with or without dalteparin studies.<sup>14</sup> A meta-analysis performed by the ASCO Venous Thromboembolism Guidelines panel, which included 11 eligible anticoagulant trials in the treatment of patients with cancer without VTE, showed a significantly decreased overall 1-year mortality with a relative risk of 0.905 (95% confidence interval, 0.85–0.97;  $p = .003$ ).<sup>15</sup> The question remains whether anticoagulant therapy should be offered to patients in the outpatient setting who lack a standard indication.<sup>10,16</sup>

### Semuloparin

The SAVE-ONCO trial was designed to evaluate the hemisynthetic, anti-Xa ultra-LMWH semuloparin in patients 18 years and older with metastatic or locally advanced cancer of the lung, pancreas, stomach, colon, rectum, bladder, or ovary who would not receive anticoagulation by current standards.<sup>4</sup> Eligible patients received subcutaneous injections of semuloparin 20 mg once daily or placebo beginning with day 1 of a course of chemotherapy that continued for the duration of the chemotherapy regimen.<sup>4</sup>

SAVE-ONCO found an absolute risk reduction difference of 2.2% in the rate of VTE events with semuloparin with no significant effect on major bleeding or mortality.<sup>4,10</sup> However, the U.S. Food and Drug Administration (FDA) Oncology Drug Advisory Committee recently

voted 14-1 against approving the drug for prophylactic prevention of VTE in cancer patients undergoing chemotherapy.<sup>17</sup> The committee denied approval based on the need for subgroup analyses to identify patients who would benefit most from prophylactic anticoagulation, the short follow-up period of 3.5 months, and the fact that not all chemotherapeutic agents have the same thrombogenic potential.<sup>15</sup> There are currently at least six additional trials that researchers hope will answer questions such as what the magnitude of the survival benefit may be and whether treatment with LMWHs affects tumor growth or dissemination.<sup>10</sup>

### New Anticoagulation Therapies

Another key controversy involves determining the role new oral anticoagulants should have in VTE prophylaxis and treatment in patients with cancer. Current agents have been studied extensively but are still far from ideal agents in patients with cancer because of multiple limitations. LMWHs are expensive and require daily subcutaneous injections. Warfarin exhibits numerous drug-food and drug-drug interactions and requires frequent international normalized ratio (INR) monitoring, which can be exceedingly difficult in patients with cancer. New anticoagulant agents have been developed to address the limitations of these traditional agents with the hope that some of the disadvantages may be overcome without compromising efficacy.<sup>7</sup>

The novel agents already on the market or in development center around two main targets: thrombin and factor Xa. Thrombin and factor Xa are both part of the common pathway for coagulation, and agents targeting either enzyme have been shown to be efficacious as anticoagulants.<sup>18</sup> However, differences still exist between the two classes of agents. Plasma clotting time is much more sensitive to small changes in thrombin concentration than factor Xa; therefore, it is reasonable to assume that factor Xa inhibitors may have a wider therapeutic range.<sup>18</sup>

### Direct Thrombin Inhibitors

There are several potential advantages to oral direct thrombin inhibitors (DTIs). Heparin is an indirect inhibitor of thrombin and is less effective in the presence of platelet-rich thrombi due to neutralization by platelet factor 4 (PF4) and high-molecular-weight multimers of von Willebrand factor released by activated platelets.<sup>18</sup> However, DTIs are able to better suppress thrombus growth because they are not affected by PF4.<sup>18</sup> There is no need for routine coagulation monitoring with the newer DTIs because they produce a more predictable anticoagulant response.<sup>18</sup>

Dabigatran etexilate is a potent and specific reversible thrombin inhibitor that directly binds to the active catalytic site of thrombin. In the coagulation cascade, thrombin converts soluble fibrinogen to fibrin and activates factors V, VIII, and XI, which serve to generate more thrombin.<sup>16</sup> Thrombin also stimulates platelets and activates factor XIII to stabilize the clot through the formation of cross-linked bonds among the fibrin molecules.<sup>16</sup> Dabigatran etexilate is a prodrug with 6% oral bioavailability, and plasma levels peak within about 2 hours.<sup>16</sup> The drug has a half-life of 12–17 hours, allowing for once or twice daily administration. Approximately 80% of the drug is excreted unchanged by the kidneys, making the drug contraindicated in patients with a creatinine clearance less than 30 mL/min.<sup>16</sup> Dabigatran is not affected

by food and has few drug-drug interactions. Although several coagulation tests, including activated partial thromboplastin time (aPTT), thrombin time, and ecarin clotting time, are prolonged in a dose-dependent fashion by dabigatran etexilate, the tests are not suitable for precise monitoring of therapy.<sup>16</sup> There is also no currently available antidote to reverse the antithrombotic effects of dabigatran etexilate in the case of overdose.<sup>15</sup>

The RE-VOLUTION clinical trial program, which features 38,000 patients worldwide, has been investigating the clinical potential of dabigatran etexilate.<sup>19</sup> Among the primary prevention trials for VTE prevention, RE-MODEL, RE-MOBILIZE, and RE-NOVATE excluded patients with active malignant disease and, although RE-NOVATE II did not specifically exclude patients with an active malignancy, it was not reported whether any patients with cancer were actually included in either treatment arm.<sup>20-23</sup> Among the treatment trials for dabigatran, RE-COVER included 64/1,273 (5%) patients with active cancer in the dabigatran arm and 57/1,266 (4.5%) patients with active cancer in the warfarin arm. Summary statistics from the trial adjusted for the presence or absence of active cancer at baseline. Results from RE-COVER2, RE-MEDY, and RE-SONATE are available and have proven noninferiority to warfarin. However, no results have been published that determine whether any conclusions can be made regarding patients with cancer who may have been included in the analyses.

## Direct Factor Xa Inhibitors

Factor Xa (FXa) is responsible for the conversion of prothrombin to thrombin in the coagulation cascade. The FXa inhibitors decrease the production of thrombin to interrupt the formation of clots. As a class, the direct FXa inhibitors have a broad therapeutic window, low patient variability, minimal food and drug interactions, and do not necessitate laboratory monitoring.<sup>17</sup>

Rivaroxaban is the only direct FXa inhibitor currently on the market in the United States. It has a bioavailability of 80% and reaches C<sub>max</sub> in 2–4 hours.<sup>16</sup> Rivaroxaban has a half-life of 12–13 hours, which allows for once daily administration. One-third of the drug is eliminated unchanged in the urine while the other two-thirds are metabolized in the liver via CYP3A4, CYP2C8, and other CYP-independent mechanisms.<sup>16</sup> Rivaroxaban must be dose adjusted in patients with renal impairment and is contraindicated in patients with a creatinine clearance <30 mL/min.<sup>16</sup> Concomitant administration of potent CYP3A4 inhibitors, such as the azoles, and p-glycoprotein inhibitors is not recommended.

Primary prevention trials for rivaroxaban included the RECORD1–RECORD4 trials and the MAGELLAN trial. The RECORD trials did not specifically exclude patients with an active malignancy, but they did not report on results in that patient population either.<sup>24-26</sup> The MAGELLAN trial compared the efficacy of rivaroxaban 10 mg PO daily for 35 days with a standard 10-day treatment of enoxaparin 40 mg SQ daily to prevent VTE in medically ill patients, including patients with active cancer. Rivaroxaban was shown to be noninferior to enoxaparin for VTE prevention and death at day 10 (2.7% versus 2.7%,  $p = .0025$  for noninferiority). At day 35 rivaroxaban was superior to enoxaparin (4.4% versus 5.7%,  $p = .02$ ). However, the bleeding rates at days 10 and 35 were higher with rivaroxaban, leading to a net clinical benefit in favor of enoxaparin. A subgroup analysis currently underway may

potentially shed light on whether rivaroxaban may be associated with a net clinical benefit in patients with active cancer.<sup>27</sup>

Treatment trials for rivaroxaban, including EINSTEIN-DVT EVALUATION, EINSTEIN PE, and EINSTEIN-EXTENSION, have compared rivaroxaban with placebo as well as enoxaparin followed by VKA for 3–12 months. EINSTEIN-DVT EVALUATION included 11/135 (8%) patients in the 20-mg arm, 14/134 (10%) patients in the 30-mg arm, 16/136 (12%) patients in the 40-mg arm, and 10/137 (7%) patients in the LMWH/VKA arm with active cancer. Eight patients with malignancy in the rivaroxaban arms died during the study period compared with three patients in the LMWH/VKA arm. EINSTEIN PE included 114/2,419 (4.7%) patients in the rivaroxaban arm and 109/2,413 (4.5%) patients in the standard therapy arm with active cancer. A Cox proportional-hazards model stratified according to the intended duration of treatment, with adjustment for the presence or absence of cancer, was performed on an intention-to-treat basis for the primary efficacy analysis. Twenty patients with malignancy who were randomized to the rivaroxaban arm died during the study period compared with 23 patients in the standard therapy arm. The EINSTEIN-EXTENSION trial did not exclude patients with cancer nor did they report results for the patients with cancer who may have been included. The results have demonstrated an 82% relative risk reduction compared with placebo and noninferiority efficacy compared with enoxaparin/VKA treatment with similar rates of bleeding between groups. However, additional data are still needed for special populations, such as patients with cancer, because they were not well-represented in these trials.

The potent, reversible direct FXa inhibitor apixaban is currently being evaluated in clinical trials in the United States for VTE prophylaxis and treatment. Apixaban is already approved in Europe for treatment of VTEs. Apixaban has high oral bioavailability and reaches C<sub>max</sub> approximately 1–3 hours following administration. Its half-life is 8–15 hours. Apixaban has a multimodal mechanism of elimination. Although most of the drug is eliminated into the feces, some is eliminated via CYP-dependent mechanisms and in the urine.<sup>16</sup>

The major trials being conducted to support apixaban for the indication of VTE prophylaxis after major orthopedic surgery include the ADVANCE 1, 2, and 3 trials; the ADOPT trial; and ADVOCATE.<sup>28-31</sup> The ADVANCE trials did not specifically exclude patients with cancer, but they did allow the investigator to decide whether to exclude a patient for any condition that was considered a contraindication to anticoagulation. ADVOCATE was a phase 2 clinical trial to evaluate apixaban in patients with metastatic cancer.<sup>16,31</sup> Patients receiving first- or second-line chemotherapy with metastatic cancer received 5 mg, 10 mg, or 20 mg of apixaban or placebo once daily for 12 weeks with primary outcome measures including the proportion of patients remaining free of major bleeding (MB), clinically relevant non-major bleeding (CRNMB), VTE, and grade  $\geq 3$  adverse events considered to be probably/definitely related to the study drug during the treatment period.<sup>30</sup> Fifty percent of the study population was male with 88% of the study population having an ECOG performance status of 0 or 1. The most common cancers were breast, colon, pancreas, and myeloma.<sup>29</sup> Results from the first 125 patients enrolled are currently available and show no MB events in patients who received 5 mg or 10 mg, two MB events in patients who received 20 mg, and one MB event in a patient who received placebo.

CRNMB occurred in one patient in the 5-mg arm, one patient in the 10-mg arm, two patients in the 20-mg arm, and 0 patients in the placebo arm. None of the patients who received apixaban at any dose experienced a thrombosis, while three patients in the placebo arm experienced a VTE. The authors concluded that apixaban was well-tolerated in patients with advanced cancer on chemotherapy with very low rates of major bleeding, thrombosis, and drug-related AEs.<sup>31</sup>

A phase 2 treatment trial, BOTTICELLI, designed to assess the efficacy and safety of three different dosages of apixaban compared with standard treatment with LMWHs or fondaparinux and VKA in the treatment of acute symptomatic DVT showed that apixaban can be given as sole treatment for DVT in a fixed dose. BOTTICELLI did include patients with documented active cancer and included 11/130 (8.5%) patients in the apixaban 5-mg arm, 6/134 (4.5%) patients in the apixaban 10-mg arm, 9/128 (7%) patients in the apixaban 20-mg arm, and 11/128 (8.6%) patients in the LMWH/VKA arm. Five patients died during the 3-month study period, all of whom had underlying malignant disease. All five patients had received apixaban during the trial. The direct causes of death were progressive malignant disease ( $n = 3$ ), possible PE ( $n = 1$ ), and suicide ( $n = 1$ ). AMPLIFY and AMPLIFY-EXT, phase 3 trials, are currently recruiting participants to further evaluate apixaban for treatment of acute symptomatic DVT.<sup>16</sup> Although there are no data from either of these trials yet, they are not specifically excluding patients with an active malignancy.

Edoxaban and betrixaban are also oral, reversible, and specific inhibitors of FXa that are currently being developed. Phase 3 primary prevention trials comparing edoxaban with enoxaparin are currently underway in Japan and Taiwan, but edoxaban does not have any FDA-approved indications in the United States yet.<sup>12</sup> To date, there has only been one phase 2 trial completed to evaluate betrixaban. The EXPERT trial was conducted in the United States and Canada and evaluated betrixaban 15 mg or 40 mg BID versus enoxaparin 30 mg BID for 10–14 days in 215 patients undergoing elective total-knee replacement. The primary efficacy endpoint was the occurrence of VTE during days 10–14. The authors concluded that betrixaban demonstrated antithrombotic activity and appeared to be well-tolerated. More studies will likely follow based on the results of the study.<sup>16</sup>

## Conclusion

The new oral anticoagulant agents appear promising due to the convenience of oral administration without the need for laboratory monitoring. However, the oral route may prove to be less than ideal in cancer patients who experience severe nausea and vomiting. It is also important to remember that, although patients with cancer are at increased risk for VTE, they are also at increased risk for bleeding. In the absence of viable antidotes for these new agents, there is always the risk that patients will become overly anticoagulated and bleed. Although clinical trials have been conducted to evaluate these novel agents in the general population, little can be directly applied to patients with cancer because they are underrepresented in those trials. Until there are more solid answers to some of these questions, the standard of care for VTE prophylaxis and treatment in patients with cancer is still LMWHs and warfarin. 

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## New Clinical Practice Guideline: Chemotherapy Dosing in Obese Patients

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As pharmacists, we are accustomed to regularly assessing medication doses to ensure patients are able to achieve maximal efficacy with minimal adverse effects. This balancing act becomes significantly more challenging when the stakes are higher, such as with chemotherapy. If you underdose a patient, you run the risk of his or her disease progressing; however, life-threatening toxicities may result from overdosing a patient. In oncology, we rely heavily on clinical trials and evidence-based medicine to establish the appropriate dose of individual chemotherapy drugs when used as single agents or in combination with other agents. Uncertainties arise when attempting to individualize chemotherapy doses, especially in our country's rapidly growing obese population. According to a study conducted in 2012, 35% of Americans are classified as obese and 6.3% fall into the morbidly obese category.<sup>1</sup>

Most chemotherapy doses are determined by calculating body surface area (BSA), which simply incorporates height and weight. In obese patients, it is common practice to calculate a BSA using an ideal

or adjusted body weight, or to arbitrarily cap the BSA regardless of the patient's actual weight. These practices are primarily based on the treating physician's comfort level and have yet to be substantiated by clinical evidence. It has been reported that as many as 40% of obese patients receive reduced chemotherapy doses,<sup>2</sup> despite evidence suggesting that inappropriate dose reductions may result in a decrease in disease-free survival (DFS) and overall survival (OS), especially when the intent of the treatment is curative.

Recently, the American Society of Clinical Oncology (ASCO) convened a panel of experts to review all available evidence and develop a practice guideline for dosing chemotherapy agents in obese patients.<sup>3</sup> The guideline was published in April 2012 and recommends that cytotoxic chemotherapy agents should be dosed based on the patient's actual weight, regardless of a patient's obesity status. The recommendation is based on a systematic review of published medical literature from the past 40 years that addresses chemotherapy dosing in obese or overweight patients. This guideline differs from previous

ASCO guidelines in that the majority of the data analyzed were extracted from subgroup analyses of retrospective reviews of randomized trials, observational studies, and registry data rather than from any prospective randomized study.

The guideline makes the following evidence-based recommendations:

- Full weight-based chemotherapy doses should be used when treating obese patients with cancer, especially in the curative setting. There is no evidence of increased toxicities (short- or long-term) when obese patients receive full weight-based doses.
- Clinical judgment should be used regarding dosing obese patients with pre-existing comorbid conditions. The same practice should be applied for these patients as for all patients, and the presence of obesity alone is not a reason to alter a treatment decision regarding chemotherapy dosing.
- Treatment-related toxicities should be handled in the same manner for obese patients as they would be for nonobese patients. Clinicians should use a consistent approach when considering dose reductions for all patients.
- If a dose is reduced due to toxicity, resuming the full weight-based dose for the next cycle should be considered, especially if a possible cause of the toxicity has been resolved (such as renal or hepatic impairment). No data exist to support the practice of employing greater dose reductions in obese patients than in nonobese patients.
- Doses determined without regard for weight or BSA (fixed or capped doses) should not be used. With the exception of a few agents, evidence does not support the use of fixed doses for cytotoxic chemotherapy. Exceptions include
  - a maximum of 2-mg vincristine is used for certain regimens due to neurotoxicity
  - carboplatin doses determined using the Calvert equation should use a maximum GFR of 125 mL/min
  - bleomycin given as a fixed dose in the BEP regimen
  - dose capping for other agents requires further research and is not recommended unless future trials indicate a beneficial effect.

### Key Points to Note

- Limited evidence exists for newer targeted agents such as tyrosine-kinase inhibitors, monoclonal antibodies, and immunotherapy. Further research is needed before a recommendation can be made for these agents.
- No data were available for dose recommendations for patients with ascites or anasarca.
- For calculation of BSA, no compelling evidence was presented that suggests one formula is superior to another. Any of the standard BSA formulas is acceptable for calculating doses.

- Comprehensive and effective communication between providers and patients is essential to successful treatment. Explanation of the reason for higher doses may be necessary.

This is the first published guideline to address the issue of appropriate dosing of chemotherapy for patients categorized as obese. The recommendations contained in this guideline should provide some clarity for practitioners when dosing chemotherapy and may potentially ease any concerns that higher doses will increase the risk for toxicities in their patients. It is important to emphasize that limiting chemotherapy doses based simply on weight or BSA in the obese population has been shown to negatively impact patient outcomes and should no longer be considered standard practice. 

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# Everolimus for the Treatment of Renal Angiomyolipomas Associated with Tuberous Sclerosis Complex

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Angiomyolipomas (AMLs) are benign tumors of the kidney. The formation of AMLs of the kidney is associated with a genetic disorder called tuberous sclerosis complex (TSC).<sup>1</sup> Benign tumors associated with TSC can also clinically manifest in the brain, heart, skin, lungs, and other organs. Approximately 55%–75% of patients with TSC are diagnosed with renal AML throughout their lifetime.<sup>1</sup> Without surgical management, the tumors can compress the kidneys, leading to bleeding or kidney dysfunction. TSC has a global prevalence of nearly 1 million people and an estimated incidence of 1 in 5,800 births.<sup>2</sup> TSC is an autosomal-dominant disorder described by mutation in tumor-suppressor genes TSC1 and TSC2. It was recognized in 2003 that downstream of TSC1 and TSC2 is the mammalian target of rapamycin (mTOR) pathway. When the second allele is lost in either the TSC1 or TSC2 gene (or second mutation), a loss of normal mTOR pathway regulation occurs and constant pathway activation results. The mTOR pathway is involved in protein synthesis that controls cell growth, cell proliferation, and the regulation of new blood vessel growth or angiogenesis.<sup>1</sup> Everolimus is an oral mTOR inhibitor with a favorable toxicity profile. For these reasons the mTOR pathway has become a focus of interest, resulting in the study of everolimus for the treatment of AML associated with TSC.

The EXIST-2 (Examining Everolimus in a Study of TSC) trial evaluated the use of everolimus in a single phase 3, prospective, international, double-blind, randomized study involving 118 patients with AML ( $n = 113$ ) or sporadic lymphangiomyomatosis ( $n = 5$ ).<sup>3,4</sup> Patients with AML who enrolled in the study had radiologic evident disease (at least one lesion  $>3$  cm) without an immediate need for surgery. Patients were randomized in a 2:1 fashion: 79 patients received everolimus 10 mg orally once daily and 39 patients received placebo. The primary outcome measured was radiologic reduction in AML volume of  $\geq 50\%$  relative to baseline with no new tumor growth. Radiologic review occurred at 12, 24, and 48 weeks and then yearly thereafter. Secondary endpoints included the time to progression of AML and the response rate observed among skin lesions, which are characteristic of TSC. After a median duration follow-up of 8.3 months, a 42% response rate was observed among patients treated with everolimus versus 0% with placebo ( $p < .0001$ ).<sup>5</sup> Median time to progression reported was significantly longer in the everolimus group (hazard ratio = 0.08;  $p < .0001$ ).

The majority of adverse effects reported in the study were grade 1 or 2, and serious adverse effects were similar in the treatment and placebo arms (20.3% versus 23.1%, respectively).<sup>4</sup> As reported in previous studies, the most common adverse effect associated with treatment was stomatitis (78% grade overall, 6% grade 3). Other grade 1 or 2 adverse effects included nausea, vomiting, diarrhea, arthralgia, and acne. Laboratory abnormalities reported included hypercholesterolemia, hypophosphatemia, and anemia ( $>50\%$ ).<sup>6</sup> A serious adverse effect of therapy is noninfectious pneumonitis, which can occur in up to 14% of

patients.<sup>7</sup> Severe cases of noninfectious pneumonitis require immediate discontinuation of therapy because fatal cases have been reported. Discontinuation due to adverse effects occurred in 3.8% of patients. These reactions included hypersensitivity reactions, convulsion, and hypophosphatemia. Treatment interruptions or dose reductions due to adverse effects occurred in 52% of patients.<sup>5</sup>

Drug interactions can be problematic with everolimus, especially among patients with TSC. The central nervous system is a common site for lesions to develop, increasing the risk for seizures.<sup>1</sup> The approval study was stratified by antiepileptic use, but no stratification results have been reported.<sup>4</sup> Everolimus is metabolized by cytochrome P450 3A4 and is a substrate of P-glycoprotein. Strong inducers and inhibitors of 3A4 should be avoided if possible. Antiepileptic drugs that are strong inducers of P450 3A4 should not be administered with everolimus; however, in patients with severe seizure disorders requiring phenytoin, carbamazepine, or phenobarbital, this may not be acceptable. In these cases the starting dose is 20 mg and close monitoring is recommended. Everolimus is supplied as a tablet in 10-mg, 7.5-mg, 5-mg, and 2.5-mg doses. Administration should occur at the same time every day with a full glass of water. Food appears to have a minimal pharmacokinetic impact. It is very important to discuss starting

## Health Policy and Advocacy Section Added to HOPA Website

The HOPA website now has a Health Policy and Advocacy section. In this section, you can learn about HOPA's health policy agenda, find information about our coalition partners, and keep up to date with policy developments relevant to hematology/oncology pharmacists and their patients. Soon you will also find a link to sign up to receive health policy updates via e-mail. Please visit [www.hoparx.org](http://www.hoparx.org) and select the Health Policy & Advocacy tab to learn more!

and stopping of new medications because moderate and strong P450 3A4 inhibitors and inducers can have a significant influence on therapeutic levels of everolimus.<sup>7</sup>

Based on the improvement in primary and secondary endpoints, the U.S. Food and Drug Administration (FDA) granted accelerated approval of everolimus on April 26, 2012.<sup>7</sup> The FDA is requiring study patients to be followed to determine the duration of response and clinical benefit, including the need for nephrectomy. 

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## Oncology Medication Safety Update, May–June 2012

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High-profile events, drug shortages, and new governmental regulations have pushed medication safety to the forefront in many institutions. There are multiple organizations that publish medication safety-related information and materials; however, the task of sifting through this information can be daunting for the practitioner who is simply searching for oncology-related safety information.

This quarterly column will summarize some of the medication safety notifications released by the Institute for Safe Medication Practices (ISMP), the U.S. Food and Drug Administration (FDA), and other organizations. In addition to the *Medication Safety Alert!* newsletter, ISMP also publishes *QuarterWatch*<sup>™</sup>, an independent publication that monitors adverse drug events reported to the FDA by manufacturers, consumers, and healthcare professionals.<sup>1</sup> Although fewer than 1% of all serious adverse drug events (ADEs) are reported to the FDA,<sup>2,3</sup> direct reporting from healthcare professionals and consumers (through the MedWatch program) often provides a unique perspective that may not be available in other reporting venues. *Serious events* are defined as those that resulted in death, permanent disability, or birth defects; involved hospitalization or other intervention to prevent harm; or were life threatening or involved other medically serious consequences.

This issue of *HOPA News's* Oncology Medication Safety Update will cover May and June 2012, including ISMP's *QuarterWatch*<sup>™</sup> report for 2011.

### May 2012

- ISMP released its annual *QuarterWatch*<sup>™</sup> report for 2011.<sup>4</sup> For more detailed information, access the report at [www.ismp.org/QuarterWatch/pdfs/2011Q4.pdf](http://www.ismp.org/QuarterWatch/pdfs/2011Q4.pdf).
  - 21,002 reports were submitted through MedWatch. ISMP estimates that 2 million serious injuries due to ADEs, including 128,000 deaths, occurred in 2011. When manufacturer reports are included, the serious injury estimate increased to 4 million.
  - The top 15 reported drugs (rank) were
    - anticoagulants: dabigatran (1), warfarin (2)
    - antineoplastics and biologic agents: carboplatin (4), cisplatin (6), cyclophosphamide (12), bevacizumab (14)
    - supportive care agents: zoledronic acid (13).
  - Hemorrhage occurred in approximately 63% of dabigatran cases and 66% of warfarin cases, with 14% and 7% of cases resulting in death, respectively. A large trial suggests that major and minor bleeding rates were similar between the two drugs; however, nearly 80% of the dabigatran reports were submitted by healthcare professionals, suggesting that the bleeding risk may be more severe or unexpected than anticipated.<sup>5</sup>

- There were no additional details regarding the events that occurred with antineoplastic agents.
- Revised labeling (full details on FDA website, [www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm306941.htm](http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm306941.htm))<sup>6</sup> for the following medications:
  - Bevacizumab: updates to adverse reactions, including congestive heart failure, hepatobiliary disorders, and gallbladder perforation
  - Denosumab: updated pregnancy category to X; medication guide amended to include pregnant women and patients with hypersensitivity to the drug as persons who should not take denosumab
  - Filgrastim: decreased bone density in certain pediatric populations, and mention of Amgen’s Pregnancy Surveillance Program in the patient package insert
  - Lenalidomide: medication guide updates, involving risk of secondary malignancies, presence of lactose as an excipient, and presence of the drug in semen
  - Pamidronate: warnings, precautions, and adverse reactions updated to include pregnancy
  - Pralatrexate: additions of severe dermatologic reactions and warnings regarding impaired renal function.

## June 2012

- ChemoPlus gowns (ISMP *Medication Safety Alert! Acute Care Edition*, June 14, 2012): During intravenous (IV) iron compounding, drug accidentally sprayed onto the gown worn by the technician and seeped into the clothing. The gown worn by the staff member, a ChemoPlus Protective Gown (Covidien), is not specifically rated to meet the recommendations for preparing or administering chemotherapy; however, ChemoPlus Poly-Coated and ChemoBloc Poly-Coated gowns are considered appropriate personal protective equipment (PPE) for chemotherapy handling.<sup>7</sup>
- Ondansetron and QT prolongation (FDA): A recent study suggests that a single 32-mg IV dose of ondansetron may predispose patients to develop Torsades de pointes. The label for the brand name product (Zofran<sup>®</sup>) has been changed to reflect the recommendation of a maximum IV dose of 16 mg. This new information does not change any recommendations for oral dosing. The study used to update the labeling is not available at this time.<sup>8</sup>
- Revised labeling (full details on FDA website, [www.fda.gov/Safety/MedWatch/SafetyInformation/ucm309380.htm](http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm309380.htm))<sup>9,10</sup> for the following:
  - Bendamustine: updates to use in pediatric populations
  - Pemetrexed: addition of esophagitis as an adverse reaction.

Because HOPA members play different roles in the continuum of oncology care, the needs for medication safety information will vary greatly. If you have any suggestions for future medication safety topics or comments on the contents of this issue, please provide feedback to *HOPA News* at [info@hoparx.org](mailto:info@hoparx.org), with “Medication Safety Column” in the subject line. 

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# Leading Stories from ASCO 2012 Annual Meeting

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The 2012 American Society of Clinical Oncology (ASCO) Annual Meeting was held June 1–5 in Chicago, IL. This year's meeting saw releases of data on significant advances in the treatment of both solid tumors and hematologic malignancies. The most exciting advances discussed during this year's meeting included investigational drugs that may come to market soon. The following is a summary of some of the highlights from the meeting.

## T-DM1 Improves Progression-Free Survival in HER2+ Breast Cancer

Trastuzumab emtansine (T-DM1) is an antibody conjugate that uses trastuzumab as a backbone for HER2-targeted delivery of the cytotoxic emtansine (DM1), which binds to tubulin, disrupting microtubule dynamics when released intracellularly. EMILLA, the phase 3 randomized trial (abstract LBA1), compared the effectiveness and safety of the T-DM1 conjugate with capecitabine plus lapatinib (XL) in 991 patients who were previously treated with trastuzumab and a taxane. Patients receiving T-DM1 had prolonged progression-free survival (PFS) compared with those patients receiving XL (9.6 month versus 6.4 months;  $p < .0001$ ). In addition, grade 3 and 4 adverse events were less frequent in the T-DM1 arm (40.8% versus 57%) as were dosage reductions and treatment discontinuation.

## Weekly Paclitaxel Better Than Some More Expensive Options

Although the best chemotherapy agent for metastatic breast cancer will likely remain a matter of debate, results from the CALGB 40502 trial (abstract CRA1002) lend some clarity to the first-line chemotherapy setting. Patients were randomized 1:1:1 to one of three arms—paclitaxel (90 mg/m<sup>2</sup>), nanoparticle albumin-bound paclitaxel (nab-paclitaxel; 150 mg/m<sup>2</sup>), or ixabepilone (16 mg/m<sup>2</sup>)—given in a 3-week-on/1-week-off schedule. The trial was closed early based on a futility analysis. Median PFS with paclitaxel, nab-paclitaxel, and ixabepilone was 10.4 months, 9.6 months, and 7.6 months, respectively. Higher rates of adverse events were reported in patients receiving both nab-paclitaxel and ixabepilone compared with those who received paclitaxel. The approval and subsequent withdrawal of approval of bevacizumab (received by 98% of the patients) occurred during the trial, complicating the interpretation of results; however, results were similar across all of the evaluated subgroups.

## Afatinib in EGFR Activating Mutation Non-Small Cell Lung Cancer

Afatinib, an irreversible ErbB1, ErbB2, and ErbB4 tyrosine kinase inhibitor, had positive data reported in the phase 3 LUX-Lung trial (abstract LBA7500). Patients had non-small cell lung cancer (NSCLC) of adenocarcinoma histology, stage 3B/4 disease, were chemotherapy naïve, and had an activating epidermal growth factor receptor (EGFR) mutation. A total of 345 patients were randomized in a 2:1 fashion to afatinib 40 mg PO daily or pemetrexed 500 mg/m<sup>2</sup> IV plus cisplatin 75 mg/m<sup>2</sup> IV every 21 days for up to six cycles. Treatment with afatinib led to an improvement in PFS of 4.2 months compared with pemetrexed plus cisplatin (11.1 months versus 6.9 months, respectively). In

the subset of patients ( $n = 308$ ) with common mutations (Del19/L858R), the improvement in PFS was more striking: 13.6 months with afatinib versus 6.9 months with chemotherapy ( $p < .0001$ ). Objective response rates were significantly higher with afatinib (56% versus 23%;  $p < .0001$ ). The most common drug-related adverse events with afatinib were diarrhea (95%), rash (62%), and paronychia (57%).

## Pemetrexed Maintenance Improves Overall Survival in Non-Squamous NSCLC

The phase 3 trial PARAMOUNT had previously reported improvements in PFS in patients with NSCLC treated with pemetrexed maintenance compared with placebo. The investigators have now reported that the secondary endpoint of overall survival (OS) has also reached statistical significance (abstract LBA7507). The PARAMOUNT trial randomized 539 patients with NSCLC with no progression after four cycles of pemetrexed and cisplatin to either pemetrexed maintenance or placebo in a 2:1 ratio. The OS after 24 months from randomization improved from 21% with best supportive care to 32% with maintenance pemetrexed.

## Regorafenib in Colorectal Cancer and Gastrointestinal Stromal Tumors

Investigators reported positive data for use of regorafenib in both chemotherapy-refractory colorectal cancer (abstract 3502) and gastrointestinal stromal tumors (GIST) refractory to imatinib and sunitinib (abstract LBA10008). In colorectal cancer, 760 patients with either progression or intolerance to previous chemotherapy were randomized to regorafenib (160 mg daily for 3 weeks on/1 week off) or placebo. OS was improved from 5 months to 6.4 months ( $p = .0052$ ), despite a minimal but statistically significant improvement in median PFS (difference of 0.2 months,  $p = .00001$ ). In GIST, 199 patients with imatinib- and sunitinib-refractory disease were randomized in a 2:1 fashion to regorafenib or placebo. The PFS was improved from a median of 0.9 months with placebo to 4.8 months with regorafenib. Crossover after progression was permitted and median OS has not been reached.

## Paclitaxel or Irinotecan for Advanced Gastric Cancer

Both paclitaxel and irinotecan are reasonable options for second-line therapy of advanced gastric cancer. The phase 3 WJOG4007 trial (abstract 4002) reported results from 223 advanced gastric cancer patients with disease progression after first-line platinum-based therapy. Patients were randomized to paclitaxel 80 mg/m<sup>2</sup> for 3 of 4 weeks or to irinotecan 150 mg/m<sup>2</sup> every 2 weeks. Although efficacy outcomes (OS, PFS, and response rates) numerically favored paclitaxel, they were not statistically different. Neuropathy occurred more frequently with paclitaxel, and anorexia occurred more frequently with irinotecan. In addition, neutropenia, anemia, and fatigue occurred less frequently with paclitaxel. The favorable toxicity profile and trends in better efficacy outcomes indicate paclitaxel as a preferable option to irinotecan.

## Abiraterone for Chemotherapy-Naive, Castrate-Resistant Prostate Cancer

For patients with metastatic castrate-resistant prostate cancer, the role of abiraterone will likely change to utilization prior to chemotherapy. The phase 3 trial COU-AA-302 randomized patients with chemotherapy-naïve metastatic castrate-resistant prostate cancer to either abiraterone 1,000 mg PO daily plus prednisone 5 mg twice daily or placebo plus prednisone (abstract LBA4518). Early on, the trial was unblinded by the data monitoring committee because improvements in PFS (not reached versus 8.3 months) and OS (not reached versus 27.2 months) were discovered for abiraterone versus placebo, respectively.

## Hematology

In hematology, there were impressive data presented regarding carfilzomib. There were also positive findings reported in updated results of the phase 3 StiL NHL1 study, evaluating bendamustine as a first-line treatment of indolent B-cell or mantle cell lymphoma (abstract 3). This study randomized 514 patients to either bendamustine plus rituximab (B-R) or CHOP-rituximab (CHOP-R). The PFS was significantly prolonged with B-R compared with CHOP-R (hazard ratio = 0.58; 95% confidence interval 0.44–0.74;  $p < .001$ ). Median PFS was

69.5 versus 31.2 months, respectively. OS did not differ in the treatment groups; however, 74 salvage treatments were initiated in the B-R group compared with 116 in the CHOP-R group. Of those 116 in the CHOP-R group, 52 patients received B-R as a salvage treatment.

## Significant Phase I Trial Efficacy for PD-1 Receptor Antibody

The programmed death (PD)-1 receptor antibody, BMS-936558, also known as MDX-1106, had promising data reported in subsets of patients treated in a large phase 1 trial. Disease responses were reported in subsets of patients with melanoma (abstract CRA2509), metastatic renal cell carcinoma (abstract 4505), and NSCLC (abstract 8582).

Although some of these data answer standing questions and will strengthen the evidence for the use of existing therapies, the release of data on agents on the verge of hitting the market is the most exciting part of this meeting. Each new therapy signals an incremental improvement in the treatment of patients with cancer and adds another therapeutic option for the fight against cancer. 

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## ASPHO Annual Meeting 2012 Highlights

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The American Society of Pediatric Hematology/Oncology (ASPHO) held their 25th Annual Conference in New Orleans, LA, May 9–12, with more than 800 medical professionals in attendance, including physicians, nurses, and pharmacists. The meeting featured 11 symposia, eight workshops, five platform sessions, and numerous young investigator sessions. The following are only some of the many pharmacy-related highlights presented at the conference.

### Thromboprophylaxis Workshop

According to 2012 American College of Chest Physicians guidelines for thromboprophylaxis in pediatric patients, there are only four specific scenarios in which thromboprophylaxis is indicated: children with central venous lines on long-term total parenteral nutrition (TPN) at home, patients with Kawasaki's Disease, hemodialysis patients, and patients with specific cardiac conditions. Although evidence-based research for benefit versus risk of thromboprophylaxis in children is very limited, newly published studies are helping to at least determine associated risk factors for deep vein thrombosis (DVT) in pediatric patients. Presentations from the workshop included "Risk Factors for In-Hospital Venous Thromboembolism in Children: A Case-Control Study Employing Diagnostic Validation" by Branchford and colleagues and "Mortality-Adjusted Duration of Mechanical Ventilation in Critically Ill Children with Symptomatic Central Venous Line-Related Deep Venous Thrombosis" by Higerson and the NACHRI PICU Focus Group.

A physician from the Children's Hospital of Philadelphia discussed a quality and safety initiative protocol established at their institution that was intended to decrease and prevent noncatheter-related DVT in patients older than 14 years of age with altered mobility. Institutional guidelines were developed for thromboprophylaxis using early ambulation, mechanical prophylaxis, or pharmacologic prophylaxis. Patients who received pharmacologic thromboprophylaxis were evaluated for a primary outcome of major bleeding; secondary outcomes included minor bleeding and clinically symptomatic thrombosis. Approximately 89 patients were enrolled during 2.5 years; nearly 75% or more of patients had three or more risk factors for DVT. Two patients experienced major bleeding. There were no episodes of noncatheter-related thrombosis, and there was only one episode of catheter-related thrombosis.<sup>1</sup>

### Relapsed Acute Lymphoblastic Leukemia (ALL) Current Therapeutic Options Workshop

Historically, relapsed ALL patients have been given re-induction therapy and then immediately taken to stem cell transplant (SCT). More recently, minimal residual disease (MRD) burden has been taken into account. MRD measures the amount of leukemia cells still present in bone marrow samples during induction therapy. Prior to sending patients directly to SCT, an additional postremission therapy treatment is now recommended to lower MRD burden prior to SCT. The current standard of care for first relapsed ALL in North America is referred

to as “triple re-induction” as seen in the Children’s Oncology Group (COG) AALL01P2, which is a 3-block course of therapy that consists of the following: block 1—vincristine, PEG-asparaginase, prednisone, and doxorubicin; block 2—5-day course of cyclophosphamide and etoposide, followed by high-dose methotrexate; and block 3—high-dose cytarabine and L-asparaginase.

The goal of the COG ALL Relapse Program is to evaluate novel agents. Epratuzumab, a humanized anti-CD22 monoclonal antibody, has been studied in COG ADVL04P2. The primary endpoint of the study, complete response (CR2) rate, was not significantly improved; however, an improvement in MRD was documented with only minimal toxicities.

Clofarabine, although not studied as part of the COG ALL Relapse Program, was granted accelerated approval by the U.S. Food and Drug Administration in 2004 for children with relapsed ALL who had failed at least two prior regimens. The speaker did state that clofarabine has produced a 30% response rate in heavily pretreated children with two or more ALL relapses and is currently used in combination with other therapies in this specific patient population.

Bortezomib, a proteasome inhibitor, is also being evaluated as part of the COG ALL Relapse Program, and when it is combined with the relapsed ALL standard of care chemotherapy regimen it can sensitize ALL cells to chemotherapy, improving cell kill and depth of re-induction. COG AALL07P1 is a phase 2 trial that is expected to be completed in August 2012. The trial is evaluating bortezomib in this setting and will hopefully demonstrate encouraging primary outcome results, improving the CR2 rate and ending re-induction block 1. Preliminary safety data toxicities have been limited to infections and episodes of typhilitis.

The next COG ALL first relapse study will include an update in the re-induction standard of care, incorporating dexamethasone and mitoxantrone, which is being adopted from the European standard, UK ALL-R3. The primary endpoint of COG AALL1221 will be 3-year event-free survival (EFS).

Other pathways and agents being evaluated in high-risk relapsed ALL patients include mTOR inhibition with temsirolimus; epigenetic modification with decitabine, vorinostat, and mitoxantrone; chemosensitization via leukemia stem cell mobilization using plerixafor (CXCR4 inhibitor); and signaling pathway inhibition with AC220 (FLT3 inhibitor) and ruxolitinib (JAK inhibitor). There also are some promising approaches being studied for second or greater relapsed ALL with immunotherapy, including blinatumomab, moximumab, and inotuzumab.

## Hematology Platform Sessions

Hematology platform topics included a review on a secondary outcome of the Baby HUG trial and a study evaluating efficacy of discontinuing penicillin prophylaxis in sickle cell patients older than 5 years of age.

The Baby HUG trial is a multicenter, randomized, double-blind, clinical trial designed to determine the safety and efficacy of hydroxyurea compared with placebo in the prevention of organ damage in sickle cell patients 1–3 years old. The findings of a cohort of the Baby HUG trial were discussed, debating whether known genetic modifiers of very young sickle cell anemia (SCA) patients or the effects

of hydroxyurea were more powerful. Hydroxyurea was shown to be a potent modifier of laboratory and clinical phenotypes—specifically pain and dactylitis—in SCA and to have a greater effect on SCA phenotypes than the genetic polymorphisms evaluated.<sup>2</sup>

Another platform presentation discussed the effects of discontinuing penicillin prophylaxis in 284 patients older than 5 years of age with HgbSS and sickle  $\beta^0$ -thalassemia. The primary outcome was to determine whether the continuation of penicillin prophylaxis after 5 years of age decreases the incidence of invasive pneumococcal disease (IPD). The secondary outcome was evaluating the incidence of hospitalizations for vaso-occlusive crisis (VOC) or acute chest syndrome (ACS). The study found no statistically significant difference in IPD rates between the two study arms; however, an increased incidence rate of VOC was shown in the penicillin continuation group. The increase in VOC was attributed to these patients having more severe disease at baseline and more parental vigilance as reflected in their decision to continue penicillin treatment in their children after 5 years of age.<sup>3</sup>

## Oncology Platform Sessions

Oncology platform presentations included updates to current COG trials and results of new therapeutic treatment options on the horizon for pediatric cancers. One platform presentation discussed targeting JAK2 and mTOR in xenograft models of ALL with overexpression of cytokine receptor-like factor 2 gene (CRLF2) with off-label use of ruxolitinib, sirolimus, and temsirolimus and showed promising results. This study was deemed important because of the low relapse-free survival rate (15%–23% of high-risk ALL patients treated on COG P9906 versus 66% for the entire population). COG 9906 is a phase 3 study that compares an augmented treatment regimen in newly diagnosed high-risk ALL patients with historical controls. The high-risk ALL patients were noted to have frequent rearrangements of CRLF2, leading to overexpression, and frequent JAK2 mutations. A mouse xenograft model of primary human ALL was used to study a subset of high-risk ALL with gene expression similar to that of Ph-positive ALL. After 4 weeks of therapy using ruxolitinib, a significant decrease in peripheral and splenic blast count was noted, and the same xenograft models showed a profound decrease in disease burden when exposed to sirolimus. Targeting JAK and mTOR pathways have also been shown to have therapeutic relevance in ALL treatment and may have a clearly defined role in the future. 

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## ISOPP XIII 2012 Symposium on Oncology Pharmacy Practice

Kellie Jones, PharmD BCOP

Clinical Associate Professor

Purdue University, College of Pharmacy, West Lafayette, IN

HOPA was well represented at the recent International Society of Oncology Pharmacy Practitioners (ISOPP) XIII Symposium on Oncology Pharmacy Practice, which took place in beautiful Melbourne, Australia, May 9–11. The symposium, which occurs every 2 years, opened with a presentation from Dr. David Currow, professor of palliative and supportive services from Flinders University, Adelaide, Australia. He discussed health professionals' responsibility to improve cancer outcomes both within individual practices and across the world. Dr. Carole Chambers, pharmacy director of Cancer Services with the Alberta Health Services in Canada, followed with a presentation discussing the Institute for Safe Medication Practices (ISMP) International Medication Safety Self-Assessment<sup>®</sup> for Oncology Practice and encouraged all members to complete the ISMP medication safety survey at their own institutions. This will help serve as a benchmark to compare individual practices to standards across the world. These presentations were a great way to kick off the meeting. If you are interested in participating in the self-assessment, the deadline has been extended to September 30, 2012 (visit <https://mssa.ismp-canada.org/oncology> to participate in the survey).

Other relevant presentations that touched on topics pertinent to our practices in the United States included a discussion on drug shortages from Dr. Johan Vandenbroucke (Belgium). Vandenbroucke offered a more global perspective on the problem of dealing with shortages across different countries and the issues faced around the world. A focus of every ISOPP Symposium is the admixture and delivery of chemotherapy to cancer patients. An interactive presentation by Rachel White, a human factors specialist for the Health Technology Safety Research team in Canada, focused on software and hardware devices specific to patient safety and processes to improve the delivery of medications to our patients.

As part of the research track, authors of the top-scoring abstracts presented their work as platform presentations. A wide variety of topics were presented, including

- “The Use of Cytotoxic Drugs in Veterinary Medicine: Prescription and Handling Practices in Portugal During 2011,” by Drs. Sara Gato and Joao Pedro (Portugal)
- “Establishment of a Pharmacist-Led Phase I Clinical Trials Program,” by Dr. R. Donald Harvey (United States)
- “Unlicensed and Off-Label Use in a Pediatric Hematology/Oncology Unit,” by Dr. Tiene Bauters (Belgium).

Dr. Carlo DeAngelis (Canada), the 2010 research grant award winner, presented his study results in the session, “A Pilot Study to Evaluate Urinary Markers of Pain Flare in Patients Undergoing External Beam Radiotherapy for the Treatment of Painful Bone Metastases.” The 2012 research grant award winners were Dr. Rosalyn Sims (United States), “The Effect of Race on the CYP3A Mediated Metabolism of Vincristine in Pediatric Patients with Acute Lymphoblastic Leukemia,” and Dr. Shereen Nabhani (United Kingdom), “Stability of Ifosfamide in Ambulatory Elastomeric Pumps.”

For those of you who have never attended an ISOPP meeting, it is a very unique experience that allows you to meet individuals from around the world who work in your same field. The meeting offers an opportunity to learn innovative concepts and practice changes and encourage international collaborations. HOPA Past President Dr. Moe Schwartz stated, “It amazes me how much we can learn from each other and how oncology pharmacy practice is so very different throughout the world, yet so very similar in many ways.” If you are interested in learning more about ISOPP, you can visit their website at [www.isopp.org](http://www.isopp.org). The next ISOPP meeting will be held in Montreal in 2014. 

# HOPA 9TH ANNUAL CONFERENCE

## SAVE THE DATE

March 20–23, 2013 | Los Angeles, CA

## Board Update

Lisa M. Holle, PharmD BCOP, HOPA President



Continued member involvement in HOPA has allowed our organization to successfully grow to nearly 1,800 members and to enjoy a yearly increase in organization membership and annual conference attendance. We hope to build on this momentum and develop mechanisms for expanding our membership and mem-

bership benefits. In addition, our dedicated committee and task force members, along with the staff and leadership, are continuing to work on the strategic plan goals.

### Education

Annual conference planning has already begun for the HOPA 9th Annual Conference, which will be held March 20–23, 2013, in Los Angeles, CA. Each year the Program Committee reviews feedback from the previous year's conference attendees to make improvements for the following year. One improvement for this year is a call for member proposals for breakout sessions, clinical pearls, and controversies in care sessions, which will provide more members with an opportunity to propose content of interest as well as to speak at the conference. In addition, two preconference boot camp sessions will be held at this year's conference: one on bone marrow transplantation and the other focusing on the most common types of cancer. Mark your calendars for annual conference, which is a great opportunity to earn more than 25 hours of oncology pharmacy-related continuing education, obtain live BCOP recertification credits, meet your HOPA leaders and staff, network with colleagues, and discuss the latest information available from our industry sponsors.

Throughout this year we will also be identifying other types of educational activities that we can offer our members and use to improve the knowledge of healthcare professionals caring for patients with cancer.

### Practice Standards

The Standards Committee is continuing to work on the development of HOPA's first clinical practice guideline, *Investigational Medicine Best Practice*, and the Oncology Pharmacy Practice Standards Task Force has completed the first draft of the *Scope of Hematology/Oncology Pharmacy Practice*. The scope of practice document is undergoing peer review and, once finalized, will be available to members for comment before it is finalized and published. I encourage each of you to review and provide feedback for the guideline because it is the first document to describe the current scope of our profession, and your comments will ensure it is accurate and timely. During the later part of 2012, members will receive reminders about member review of this document via e-mail updates and website announcements.

### Advocacy

The Legislative Affairs Committee has been renamed the Health Policy Committee and has a new structure. The five-member committee will have additional workgroups that are each assigned to complete a specific task during this year. The name and committee structure changes reflect HOPA's commitment to health policy advocacy and our desire to get more members involved in these important efforts. To keep members and the public aware of the health policy-related efforts in which HOPA becomes involved, we've created a dedicated website page. I urge you to visit and review the letters we've signed onto (letters that have been sent to regulatory or legislative groups stating our concerns about proposed or current rules, regulations, or laws), issue briefs (summaries of HOPA's position on certain health policy-related issues), the coalitions to which we belong, and other important health policy information. Visit [www.hoparx.org](http://www.hoparx.org) and select Health Policy & Advocacy in the menu bar.

In early June, Sarah Scarpace (Health Policy Committee Chair), Niesha Griffith (President-Elect and Health Policy Committee member), Karen Nason (HOPA Executive Director), Kristin Pulatie (HOPA Health Policy and Advocacy Manager), and Jeremy Scott and Erin Morton of Drinkle Biddle and Reath LLP (our health policy consultant team) met with executive and staff leaders from the National Coalition of Cancer Research, Oncology Nursing Society, and the Susan G. Komen Foundation. These meetings were aimed at introducing ourselves and our health policy advocacy agenda (educating legislators and the public about our organization and our own health policy efforts) to some of the largest oncology-related organizations. We will continue to participate in meetings such as these during the next year.

### Industry Relations Council

Two years ago we introduced our Industry Relations Council (IRC) as a mechanism to build stronger ties with our industry partners. We now have five members: Amgen, Bristol-Myers Squibb, Celgene Corporation, Eisai, and Millenium: The Takeda Oncology Company. We held our 2nd Annual Industry Relations Council Summit in July in Glenview, IL, during which we discussed the current state of HOPA in relation to the strategic plan. We also conducted roundtable discussions regarding (1) patient assistance programs, (2) hospital formulary management, and (3) working with hospital pharmacy departments to gain a better understanding of how industry and hematology/oncology pharmacists can work together in these areas.

## Foundation

The HOPA Foundation announced its research grant in May. Seventeen HOPA members submitted letters of intent. After thorough review, eight have been invited to submit full proposals. The Research Grant Review Committee is reviewing the grant submissions, and grant awardees will be notified in November.

In addition to working on the activities listed above related to our strategic plan, the IRC, and the foundation, committees have been working diligently on various tasks that are important to the

sustainability and growth of our association. We are also excited to welcome several new staff members to HOPA who bring extensive experience in their respective areas (to learn more about them, read their profiles on page 23). The board continues to receive training and use best practices of association management in performing our board activities. The past 9 years of HOPA's existence have been eventful. We feel very fortunate to have such an active membership and wouldn't be where we are today without our nearly 1,800 members. Thank you and we look forward to the year ahead.

## HOPA's Colleague Recruitment Program

Refer a member today!



### WHEN YOU RECRUIT A COLLEAGUE, YOU

- strengthen the HOPA community
- provide greater recognition of the oncology pharmacy profession
- improve education and networking opportunities for all members
- enhance your colleagues' careers.

### FROM NOW THROUGH **DECEMBER 1, 2012**, YOU WILL RECEIVE THE FOLLOWING REWARDS

- One free month of membership added to your existing membership
- One entry into a drawing to win one of the following three prizes:
  1. Complimentary registration to the 2013 Annual Conference in Los Angeles, CA
  2. Travel grant for \$250 to the 2013 Annual Conference in Los Angeles, CA
  3. One free year of HOPA membership.

Visit [www.hoparx.org](http://www.hoparx.org) for complete program details and information about how to get credit for your referral.

Help make HOPA's voice in the industry stronger by encouraging your oncology pharmacy colleagues to become HOPA members too.

### ATTENTION GROUP DISCOUNT MEMBERSHIP PARTICIPANTS

At the end of 2012 HOPA will discontinue the group discount option. Phasing out a discount program is never an easy decision, and HOPA apologizes for any inconvenience this may cause.

HOPA, however, is offering all group members the option of renewing their membership at the current group discounted rate until December 31, 2012. Your renewed membership will go into effect at the time your current membership expires.

Please keep in mind that HOPA does offer other discount programs. You can take advantage of the multiyear discount, which offers a 5% discount when you renew for 2 years. Also, members who participate in the colleague recruitment program get a free month for every referral who joins HOPA.

If you have any questions regarding this announcement, please contact HOPA Member Services at 877.467.2791.

### HOPA MEMBERSHIP

is a valuable investment in your professional future and is continually improving benefits for its members. Be sure to take advantage of all your benefits of membership, which include

- discounted HOPA Annual Conference registration; save the date for the 2013 HOPA Annual Conference, March 20–23, in Los Angeles, CA
- members-only travel grants and recognition awards
- access to HOPA's member Listserv, our exclusive discussion forum
- participation in building HOPA and advancing oncology pharmacy practice through volunteering on committees, task forces, and work groups
- free subscription to *HOPA News*, the association's quarterly newsletter
- free job posting in the Career Center
- access to the members-only section of HOPA's website, featuring an exclusive online member directory.

## Carfilzomib (Kyprolis)

**Class:** Proteasome inhibitor

**Indication:** Relapsed and refractory multiple myeloma in patients who have received at least two prior lines of therapy, including a proteasome inhibitor and immunomodulatory agent

**Dose:** Cycle 1: 20 mg/m<sup>2</sup>/day on days 1, 2, 8, 9, and 16 to be given every 28 days; Cycle 2: if well-tolerated during first cycle, may increase dose to 27 mg/m<sup>2</sup>/day on the same schedule; utilize actual body weight; cap BSA at 2.2 m<sup>2</sup>; dose adjustments do not need to be made for weight changes <20%.

**Dose modifications:** Modify or hold doses based on toxicity: hematologic, cardiac, pulmonary, hepatic, renal, and peripheral neuropathy.

**Common adverse effects:** Fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, and pyrexia

**Serious adverse effects:** Cardiac arrest, congestive heart failure, myocardial ischemia, pulmonary hypertension, pulmonary complications, infusion reactions, tumor lysis syndrome, thrombocytopenia, hepatic toxicity, and hepatic failure

**Drug interactions:** Primarily metabolized via peptidase and epoxide hydrolase activities; unlikely to be affected by concomitant administration of CYP450 inhibitors and inducers; not expected to influence exposure of other drugs

## Accelerated FDA Approval of Kyprolis (Carfilzomib) for Multiple Myeloma

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According to the SEER database, it is estimated that 21,700 people will be diagnosed with multiple myeloma and 10,710 will die from this disease in 2012.<sup>1</sup> There are seven agents approved for the treatment of myeloma, making several treatment options available.<sup>2</sup> Unfortunately, patients may become resistant or intolerant to the currently approved treatment options. On July 20, 2012, the U.S. Food and Drug Administration (FDA) approved Kyprolis (carfilzomib) as an additional treatment option for patients with relapsed and refractory myeloma who have already received at least two prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent.<sup>3</sup> Carfilzomib is a novel proteasome inhibitor belonging to the epoxyketone class. It irreversibly binds to active sites of the 20S proteasome within the 26S proteasome, inhibiting normal proteasome activity and thus leading to apoptosis.<sup>4,5</sup> It is structurally and mechanistically unique and has potent activity in bortezomib-resistant patients with multiple myeloma.<sup>5</sup>

The approval of carfilzomib was based on several phase 1 and 2 studies evaluating its safety and efficacy in the treatment of myeloma. The first phase 2 study, PX-171-003-A0, was an open-label, single-arm study designed to evaluate carfilzomib activity in 46 patients with multiple myeloma who relapsed from >2 prior therapies (bortezomib and at least one immunomodulatory agent) and were refractory to their last treatment. Patients included in the study had received a median of five prior therapies (range 2–15). Thirty-nine patients completed at least one cycle of carfilzomib and were evaluated for response. Patients received a median of three cycles (range 1–12) of carfilzomib 20 mg/m<sup>2</sup>/day on days 1, 2, 8, 9, 15, and 16 every 28 days for up to 12 cycles. The clinical benefit response (CBR: minimal response [MR] or better) was achieved in 26% (10/39) of patients, including five PR (partial response) and five MR. Of note, five bortezomib-refractory patients achieved MR or PR. The median TTP was 6.2 months with a median duration of response (DOR) of 7.4 months. The most common adverse events documented in this trial were fatigue, anemia, thrombocytopenia, nausea, upper respiratory infection, increased creatinine, and diarrhea. Worsening of peripheral neuropathy was rare with <10% of patients experiencing this side effect.<sup>6</sup>

Based on the results of the first study, the trial was expanded to enroll an additional 250 patients at an escalated dose. In this phase 2b trial, PX-171-003-A1, patients were given carfilzomib on days 1, 2, 8, 9, 15, and 16 every 28 days with the cycle 1 dose being 20 mg/m<sup>2</sup>/day and cycles 2–12 doses at 27 mg/m<sup>2</sup>/day. Patients who completed 12 cycles were eligible to enter an extension trial to assess long-term effects of carfilzomib therapy. Two hundred fifty-seven of 266 patients enrolled were evaluated for the primary endpoint of overall response rate (ORR). The ORR was 24% with a median DOR of 7.4 months (95% confidence interval [CI] 6.2–10.3). The observed CBR was 36%, and the median DOR was 6.3 months. An additional 32% (83) of patients achieved stable disease for at least 6 weeks. Two hundred twenty-nine patients were evaluated for cytogenetic abnormalities. Of those, 71 had >1 abnormality and achieved an ORR of 28% with median DOR of 7 months (95% CI 4–10). For all patients included in the study, the median overall survival (OS) was 15.5 months (95% CI 12.7–19). The patients included were all heavily pretreated with a median of five (range 1–20) prior treatment lines containing a median of 13 antimyeloma agents. The most commonly reported treatment emergent > grade 3 adverse events were primarily hematologic and included thrombocytopenia (22%), anemia (20%), lymphopenia (10%), pneumonia (8%), neutropenia (8%), fatigue (7%), hyponatremia (5%), and hypercalcemia (5%). There were rare occurrences of new onset peripheral neuropathy or > grade 3 neuropathy (<1%) despite 77% (206) of patients having grade 1–2 peripheral neuropathy at baseline.<sup>7–9</sup>

Additional studies have been conducted to assess carfilzomib's efficacy such as the PX-171-004 trial, which evaluated carfilzomib in bortezomib-naïve patients with relapsed disease. Also there was a phase 1b study of carfilzomib with lenalidomide and low-dose dexamethasone in patients with relapsed and refractory myeloma to further investigate the potential for synergy between these medications.<sup>10</sup> Onyx has ongoing trials, including the ENDEAVOR trial, which is a

phase 3, global head-to-head study comparing carfilzomib and low-dose dexamethasone to bortezomib with low-dose dexamethasone.<sup>2</sup>

Carfilzomib is administered as an intravenous infusion over 2 to 10 minutes on 2 consecutive days each week for 3 weeks (days 1, 2, 8, 9, 15, and 16) followed by a 12-day rest period to complete a 28-day cycle. The recommended starting dose for cycle 1 is 20 mg/m<sup>2</sup>/day and, if tolerated, may be increased to 27 mg/m<sup>2</sup>/day for cycles 2 and beyond. An important caveat to note while dosing is that the body surface area should be calculated based on actual body weight but capped at 2.2 m<sup>2</sup>. Carfilzomib is supplied as a 60-mg single-use refrigerated vial that should be kept in its original package to be protected from light. Reconstitute each vial with 29 mL of sterile water to create a 2-mg/mL solution. The appropriate dose should be removed from the vial and diluted in a 50-mL intravenous bag of 5% dextrose. The compounded preparation is stable for 24 hours refrigerated and 4 hours at room temperature.<sup>3</sup>

The administration of carfilzomib requires hydration (250–500 mL) before and after each dose in cycle 1 to decrease the risk of renal injury and tumor lysis syndrome (<1%). For subsequent cycles, hydration may be administered as needed. Infusion reactions may occur immediately following or up to 24 hours after administration of carfilzomib. It is recommended to premedicate with dexamethasone orally or intravenously prior to all doses during cycle 1 and during the first cycle of the dose escalation to prevent or lessen the severity of infusion reactions, the symptoms of which may include fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina.<sup>3</sup> It is important to educate patients on the potential for this delayed infusion reaction.

There are no contraindications to administering carfilzomib; however, precautions or dose adjustments must be implemented when certain patient-specific conditions occur, particularly grade 3 or 4 conditions. Death due to cardiac arrest associated with carfilzomib use has been reported in three patients. Other cardiac effects were observed in approximately 7% of patients during the studies and included new-onset congestive heart failure, pulmonary edema, and ejection fractions that had decreased from baseline. Patients with New York Heart Association Class III and IV heart failure, myocardial infarction within the previous 6 months, or conduction abnormalities uncontrolled by medications were excluded from clinical trials. Pulmonary hypertension is another severe but rare side effect associated with carfilzomib administration. It was reported in 2% of patients but was >grade 3 in <1% of patients. Additional pulmonary complications such as dyspnea were reported in 35% of patients enrolled in clinical trials, yet there were 5% of patients with grade 3 dyspnea, no grade 4 events, and one documented death.<sup>2,3,11</sup>

Thrombocytopenia is a known side effect of carfilzomib with nadirs occurring around day 8 of each cycle with recovery to baseline by the start of the next cycle. Grade 4 thrombocytopenia was experienced by 10% of patients in trials, with 36% of patients experiencing any grade. One percent of patients required a dose reduction due to this toxicity with <1% of patients discontinuing treatment for this adverse event.<sup>2,3,11</sup>

Grade 3 or 4 hepatic toxicities, including increases in transaminases

and bilirubin, typically resolve when the drug is held. In <1% of patients, fulminant hepatic failure has been documented. Liver enzymes should be monitored frequently in patients receiving carfilzomib. Patients with baseline liver dysfunction (ALT/AST > 3 x upper limit of normal [ULN] and bilirubin > 2 x ULN), were excluded from the clinical trials, therefore administration in this population has not been evaluated.<sup>2,5</sup>

Because renal dysfunction is fairly common (>50%) in patients with myeloma, an open-label phase 2 study (PX-171-005) was conducted to assess carfilzomib in patients with renal impairment. Thirty-nine patients were included in the study: ten with normal renal function (creatinine clearance [CrCl] >80 mL/min), nine with mild renal impairment (CrCl 50–79 mL/min), nine with moderate renal impairment (CrCl 30–49 mL/min), nine with severe renal impairment (CrCl <30 mL/min), and two requiring hemodialysis. Patients were administered carfilzomib 15 mg/m<sup>2</sup>/day on days 1, 2, 8, 9, 15, and 16 every 28 days for cycle 1, carfilzomib 20 mg/m<sup>2</sup>/day in cycle 2, and carfilzomib 27 mg/m<sup>2</sup>/day in cycle 3. Based on the pharmacodynamic/pharmacokinetic analysis, it appears safe to administer carfilzomib in patients with renal insufficiency without dose adjustment. It is advisable to administer carfilzomib after dialysis because carfilzomib concentrations have not been studied in the dialysis setting.<sup>3,12</sup>

Intravenous carfilzomib administration does not result in medication accumulation as evidenced by similar AUCs (area under curve/systemic exposure) and half-lives on days 1 and 15 or 16 of cycle 1. There is also a dose-dependent increase in exposure as the carfilzomib dose is increased between 20 mg/m<sup>2</sup> and 36 mg/m<sup>2</sup>. The mean steady state volume of distribution of carfilzomib 20 mg/m<sup>2</sup> was 28 L. Based on in vitro data, the binding of carfilzomib to human plasma proteins averaged 97% with a concentration range of 0.4 to 4 micromolar. Carfilzomib is rapidly metabolized by peptidase and epoxide hydrolase; therefore it is unlikely to be affected by concomitant administration of cytochrome (CYP) p450 inhibitors and inducers because the CYP p450-mediated mechanisms play a minor role in the drug's metabolism. Based on its pharmacokinetic profile, it is not theorized to impact the exposure of other drugs. The metabolites of carfilzomib are not known to have any biologic activity. Carfilzomib is a P-glycoprotein (P-gp) substrate, but due to its pharmacokinetic profile, it is unlikely to be affected by P-gp inhibitors or inducers. Carfilzomib is rapidly eliminated with a half-life of <1 hour on day 1 of cycle 1. Systemic clearance ranged from 151–263 L/hr and exceeded hepatic blood flow supporting extrahepatic clearance of carfilzomib. Age does not appear to impact exposure based on analysis of population pharmacokinetic data in patients older or younger than 65 years. There was also no major difference between AUC and C<sub>max</sub> values between male and female patients.<sup>3,10</sup>

Patients should be counseled on the risk of infusion reactions and advised to avoid dehydration by maintaining adequate fluid intake. Patients should notify their physician if they develop fever, chills, rigors, chest pain, cough, or swelling of the feet or legs. Women of reproductive potential should use effective contraceptive measures to prevent pregnancy during treatment and avoid breast-feeding. 

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HOPA UNIVERSITY

## The Science of Education

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Val R. Adams, PharmD FCCP BCOP; Sara K. Butler, PharmD BCPS BCOP

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Russell S. Crawford, BPharm BCOP; Stephanie S. Minich (Taber), PharmD BCOP

Visit [www.hopau.org](http://www.hopau.org) for more details and to access sessions.



## Pazopanib (Votrient™)

**Class:** Tyrosine kinase inhibitor; vascular endothelial growth factor (VEGF) inhibitor

**Indication:** Advanced soft tissue sarcoma patients who have received prior chemotherapy

**Dose:** 800 mg orally once daily (four 200-mg tablets) without food at least 1 hour before or 2 hours after a meal

**Dose modifications:** 200 mg orally once daily for patients with moderate hepatic impairment

**Common adverse effects:** The most common adverse effects in patients with soft tissue sarcoma are decreased appetite, decreased weight, diarrhea, dysgeusia, dyspnea, fatigue, hair color changes, headache, hypertension, musculoskeletal pain, nausea, skin hypopigmentation, tumor pain, and vomiting.

**Serious adverse effects:** There is a black box warning that severe and fatal hepatotoxicity has been observed in clinical trials. Hepatic function should be monitored and pazopanib therapy should be interrupted, reduced, or discontinued as recommended. Other serious adverse effects include QT prolongation and Torsades de pointes, cardiac dysfunction, hemorrhagic events, arterial and venous thrombotic events, gastrointestinal perforation and fistula, reversible posterior leukoencephalopathy syndrome, hypertension, infection, and increased toxicity with other cancer therapies.

**Drug interactions:** CYP3A4 inhibitors: avoid use of strong inhibitors; CYP3A4 inducers: consider an alternative medication or avoid pazopanib; CYP substrates: avoid use of concomitant medications with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8; concomitant use with simvastatin increases the risk of ALT elevations—usage should be monitored closely and with caution.

## Pazopanib for Advanced Soft Tissue Sarcoma

Jamie K. Joy, PharmD

Pharmacy Clinical Coordinator

Cancer Treatment Centers of America Western Regional Medical Center,  
Goodyear, AZ

Soft tissue sarcomas are the most common type, making up approximately 80% of all sarcomas. Sarcomas themselves are a heterogeneous group of tumors because there are more than 50 histological subtypes, which is challenging when making treatment decisions about these tumor types. The most common primary sites for soft tissue sarcomas are extremities, the trunk, retroperitoneum, and the head

and neck.<sup>1</sup> Patients with metastatic soft tissue sarcoma generally have a median overall survival (OS) of 12 months.<sup>2</sup> Pazopanib has previously been approved for the treatment of advanced renal cell carcinoma; however, in April 2012 the U.S. Food and Drug Administration (FDA) approved pazopanib for the treatment of advanced soft tissue sarcoma previously treated with chemotherapy.<sup>3</sup> Pazopanib is a multityrosine kinase inhibitor of vascular endothelial growth factors (VEGF) 1, 2, and 3 and platelet-derived growth factor receptor  $-\alpha$  and  $-\beta$ . In vivo, pazopanib has exhibited angiogenesis activity.<sup>4</sup> The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for soft tissue sarcoma recommends pazopanib for palliative therapy for soft tissue sarcoma of the extremities, trunk, head and neck, retroperitoneum, or intra-abdominal.<sup>5</sup>

Pharmacokinetic data show that when pazopanib tablets are crushed, the bioavailability and rate of absorption are increased. Therefore, it is not recommended to crush the tablets for administration. In addition, systemic absorption is increased by approximately twofold when pazopanib is taken with food. It is recommended that pazopanib be taken without food at least 1 hour before or 2 hours after eating food. In vitro studies show that pazopanib is metabolized by CYP3A4 with minor contribution from CYP1A2 and CYP2C8. The half-life of pazopanib is 30.9 hours, and pazopanib is highly bound to plasma proteins. Elimination of pazopanib occurs mainly via the feces, with less than 4% eliminated renally.<sup>4</sup>

In the PALETTE trial—which was a multicenter, international, phase 3 study—369 patients were randomized to receive pazopanib 800 mg orally daily ( $n = 246$ ) or placebo ( $n = 123$ ). Patients had been treated with at least one regimen containing an anthracycline and had a maximum of four previous lines of systemic chemotherapy. Patients were included only if they had one of the common soft tissue sarcoma diagnoses. The primary endpoint of the study was progression-free survival (PFS) and the secondary endpoints were OS, response rate, safety, and quality of life. The results of this study showed a median PFS of 4.6 months for pazopanib compared with 1.6 months for patients treated with placebo ( $p < .0001$ ). OS was 12.5 months for patients treated with pazopanib compared to 10.5 for placebo (not statistically significant). There was a higher percentage of treatment interruptions in the pazopanib group (48%) versus placebo (9%). Adverse reactions were similar to what has been reported in renal cell carcinoma patients; however, there seemed to be a higher incidence of gastrointestinal (GI)-related side effects in sarcoma patients compared with renal cell carcinoma patients. Of note, there was a higher percentage of patients with elevated liver function test levels (aspartate aminotransferase/alanine aminotransferase [AST/ALT]) when taking pazopanib. There were some serious adverse reactions that occurred during the study, specifically pneumothorax, cardiotoxicity, and venous thromboembolic events. There was no difference between the groups regarding quality of life. The PALETTE trial was integral in the FDA's decision to approve for pazopanib for the treatment of soft tissue sarcoma.<sup>2,6</sup>

The most common side effects of pazopanib are GI related: decreased appetite, diarrhea, nausea, and vomiting. Other common side effects in patients with soft tissue sarcomas are decreased weight,

hypertension, tumor pain, skin hypopigmentation, and hair discoloration. Some of the more common side effects differ among patients with renal cell carcinoma versus soft tissue sarcoma.<sup>4</sup>

There are also many warnings and precautions for pazopanib in the package insert. The first is a black-box warning for hepatotoxicity. Increases in serum transaminases and total bilirubin have been observed. Serious cardiotoxic warnings include prolonged QT intervals, Torsades de pointes, congestive heart failure, and decreased left ventricular ejection fraction (LVEF). Fatal hemorrhagic events, arterial thrombotic events, venous thromboembolic events (VTE), and GI perforation or fistula have occurred. Reversible posterior leukoencephalopathy syndrome has been observed. Hypertension, hypothyroidism, proteinuria, and infection are also serious adverse reactions of pazopanib therapy.<sup>4</sup>

Dosing of pazopanib is 800 mg orally daily without food. Dosing modifications are recommended for patients with moderate hepatic impairment (defined as a total bilirubin  $>1.5$ – $3 \times$  the upper limit of normal, regardless of ALT value). Patients with moderate hepatic impairment can take pazopanib 200 mg orally daily without food. Pazopanib is not recommended for patients with severe hepatic impairment. No dose modification is recommended for renal impairment. Dose modifications may be necessary due to tolerability, and the manufacturer recommends decreasing or increasing in 200-mg steps based on individual tolerability. Pazopanib has not been studied in patients younger than 18 years old and is currently indicated only for adult patients.<sup>4</sup>

Specific monitoring should be done during pazopanib therapy. Liver function tests should be checked at baseline, at least once every 4 weeks for the first 4 months of therapy, and then periodically. Baseline and periodic monitoring of electrocardiograms (ECG), electrolytes, and LVEF evaluation should be done. Blood pressure should be well controlled prior to starting pazopanib and should be checked in the first week of therapy and then frequently thereafter. Baseline urinalysis and periodic urinalysis and thyroid testing should be monitored.<sup>4</sup>

There is a high likelihood of many important potential and actual drug-drug interactions with pazopanib. When CYP3A4 inhibitors are concomitantly given with pazopanib, the dose of pazopanib should be reduced or the combination of a strong CYP3A4 inhibitor and pazopanib should be avoided. CYP3A4 inducers and CYP substrates (specifically medications that are metabolized by CYP3A4, CYP2D6, and CYP2C8) are not recommended with concomitant pazopanib therapy. Simvastatin and pazopanib concomitant therapy should be closely monitored and only used with caution because this combination has an increased risk of ALT elevation. It is important to counsel patients about the potential for drug-drug interactions with pazopanib therapy and to take a thorough medication history during therapy.<sup>4</sup>

### Patient Counseling Points

Pazopanib is supplied in 200-mg tablets, so patients on a full dose would take four of the 200-mg tablets for each dose by mouth daily. Pazopanib is available in a bottle of 120 tablets, which is approximately a 1-month supply for patients on full dosing. Pazopanib is to be taken on an empty stomach 1 hour before or 2 hours after eating food.

Patients should be counseled to follow-up with recommended monitoring such as blood pressure, liver function, thyroid, UA, ECG, and ECHO testing. Patients should be specifically educated to report any abnormal bleeding or signs or symptoms of arterial or VTE, worsening neurological function, gastrointestinal perforation or fistula, or infection. Pazopanib should be stopped 7 days prior to a planned surgery because it can impair wound healing. Patients should be advised of the side effects listed previously, including the depigmentation of hair or skin, and the most common side effects (diarrhea, nausea, vomiting) and how to properly manage them.<sup>4</sup>

Pazopanib offers another treatment option for advanced soft tissue sarcomas. It is also another therapy option available in an oral formulation that offers both advantages and disadvantages. Specifically, adherence is key for its optimal efficacy. There are also many adverse effects, both common and serious, which may require dosage interruptions or modifications. It is essential to ask patients at regular intervals about signs and symptoms of these effects. There are also many parameters that need to be regularly monitored as with any chemotherapy regimen. It is essential to regularly monitor for the many potential drug-drug interactions and educate patients about them. According to the NCCN guidelines, pazopanib is a category 2A treatment recommendation. There are questions about its overall clinical benefit because the PALETTE trial did not show a difference in OS or quality of life, using instead PFS as its main endpoint. It should only be considered as a treatment option in patients with soft tissue sarcomas of the extremities, intra-abdominal area, trunk, retroperitoneum, or head and neck location who have previously received chemotherapy. In addition, it may be a more attractive option to patients who would prefer an oral formulation; however, the caveat to this is that GI-related side effects are quite common and may result in treatment interruptions that will affect its optimal efficacy.<sup>2,6</sup>

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## Pertuzumab (Perjeta™)

**Class:** Human epidermal growth factor receptor (HER) dimerization inhibitor

**Indication:** Use in combination with trastuzumab and docetaxel in patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy.

**Initial dose:** 840 mg as intravenous (IV) infusion over 60 minutes

**Maintenance dose:** 420 mg as IV infusion over 30 to 60 minutes every 3 weeks

### Dose modifications

- The loading dose of 840 mg should be repeated if more than 6 weeks occur between previous pertuzumab doses.
- Withhold pertuzumab and trastuzumab dosing for at least 3 weeks for either
  - a drop in left ventricular ejection fraction (LVEF)
  - LVEF of 40%–45% with a 10% or greater absolute decrease below pretreatment values.
- Dose reductions for pertuzumab are not recommended.

**Common adverse effects:** Diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy

**Serious adverse effects:** Infusion-related reactions, embryo-fetal toxicities, and left ventricular dysfunction

**Drug interactions:** None listed

## Pertuzumab: A ME-too HER2 or a Novel Approach to the Treatment of Metastatic Breast Cancer?

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HER2-positive breast cancer accounts for 25%–30% of breast cancers and is associated with a more aggressive disease and poorer outcomes.<sup>1</sup> With the development of the humanized monoclonal antibody trastuzumab (Herceptin®), the treatment of HER2-positive disease has seen significant improvements in survival in patients with both HER2-positive metastatic and early-stage disease. Despite these advancements in the treatment of HER2-positive disease, many patients

eventually relapse and succumb to their disease.<sup>1</sup> The newest development in the treatment of HER2-positive breast cancer is combining pertuzumab (Perjeta™) with trastuzumab and chemotherapy.

Pertuzumab is the first HER dimerization inhibitor approved by the U.S. Food and Drug Administration (FDA; June 2010). Dimerization between receptors of the HER family, including HER1 (epidermal growth factor receptor), HER2, HER3, and HER4, is a crucial step in the activation of pathways critical for angiogenesis, cell survival, migration, apoptosis, and proliferation. Inhibiting different epitopes of the HER2 extracellular domain with trastuzumab (domain IV) and pertuzumab (domain II) results in a more comprehensive blockade of HER2 signaling. Pertuzumab also prevents dimerization between HER2 and HER3, a pathway vital for the activation of the phosphatidylinositol 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) pathway.<sup>2-4</sup>

Pertuzumab gained approval based on the results of the clinical evaluation of pertuzumab and trastuzumab (CLEOPATRA) study—a phase 3, randomized, double-blind, placebo-controlled, multinational trial. The CLEOPATRA trial assessed the combination of pertuzumab, trastuzumab, and docetaxel compared to trastuzumab and docetaxel in chemotherapy- and biologic therapy-naive HER2-positive patients with metastatic breast cancer. Patients were excluded if they had an ECOG performance status of 2 or greater, left ventricular ejection fraction of <50% at baseline, central nervous system metastases, or exposure to a cumulative dose of doxorubicin of 360 mg/m<sup>2</sup> or equivalent. Patients were still eligible to participate if they had received prior therapy with one hormonal therapy before randomization or if they had received adjuvant or neoadjuvant chemotherapy with or without trastuzumab more than 12 months between the completion of the therapy and diagnosis of metastatic breast cancer. The primary outcome measured was progression-free survival (PFS) as assessed by independent review. Secondary outcomes included overall survival (OS), PFS assessed by study investigators, objective response rate (ORR), and safety.<sup>5</sup>

A total of 808 patients were randomized in a 1:1 fashion to receive pertuzumab, trastuzumab, and docetaxel or placebo, trastuzumab, and docetaxel. The median duration of therapy was 18.1 months in patients receiving combination therapy with pertuzumab and 11.8 months in patients receiving trastuzumab and docetaxel alone. PFS was significantly increased in patients who received pertuzumab compared to those who received placebo (18.5 months versus 12.4 months; hazard ratio [HR] 0.62; 95% confidence interval [CI] 0.51–0.75;  $p < .001$ ). The results for investigator-assessed PFS were similar to those produced in the independent review. This benefit was not seen in patients older than 75 years of age and those with nonvisceral disease. OS was increased in the pertuzumab arm (HR 0.64; 95% CI 0.47–0.88;  $p = .005$ ); however, this did not meet investigators' predefined definition of significance for this analysis. ORR was higher in the combination arm including pertuzumab (80.2% versus 69.3%;  $p = .001$ ). The most common side effects during combination therapy with pertuzumab included diarrhea (67%), alopecia (61%), neutropenia (53%), nausea (42%), fatigue (38%), rash (34%), decreased appetite (29%), peripheral

edema (23%), and febrile neutropenia (14%). Left ventricular dysfunction occurred in 4.4% of patients treated with pertuzumab compared with 8.3% of patients in the placebo group.<sup>5,6</sup>

Patients' left ventricular function (LVF) should be assessed before initiating and at regular intervals during treatment. If LVF drops below 40%, or is 40%–45% with >10% decrease from initial pretreatment values, both trastuzumab and pertuzumab should be held for at least 3 weeks and patients should be reassessed before reinitiating therapy. Patients should also be monitored for hypersensitivity reactions during the infusion, 60 minutes after the first infusion, and 30 minutes after subsequent infusions. Patients should be redosed with an initial dose of 840 mg if more than 6 weeks have passed since the last pertuzumab dose. If docetaxel therapy is discontinued, therapy may continue with pertuzumab and trastuzumab alone. If trastuzumab is discontinued, pertuzumab therapy must be discontinued.<sup>6</sup>

Pertuzumab is a novel monoclonal antibody shown to improve PFS in patients with metastatic breast cancer when used in combination with trastuzumab and docetaxel. The approval of pertuzumab has expanded the options for patients with HER2-positive breast cancer, allowing for a better fit for patients as the role of pertuzumab continues to be explored and expanded. However, with wide use of trastuzumab in the adjuvant setting, many patients may not be eligible for treatment with pertuzumab because patients were excluded from the CLEOPATRA trial if biological therapy had occurred within 12 months of enrollment.

The benefits of using pertuzumab in the treatment of a variety of patients, including those with locally advanced disease or those recently treated with biological therapy, requires further investigation. A phase 2 study by Cortes and colleagues compared pertuzumab monotherapy to combination therapy with pertuzumab and trastuzumab in patients with metastatic breast cancer. Dual therapy demonstrated superior response in a combination of pertuzumab and trastuzumab compared with pertuzumab alone.<sup>7</sup> Gianni and colleagues assessed combination pertuzumab, trastuzumab, and docetaxel in the neoadjuvant setting. The results from this phase 2 trial demonstrated a higher pathological response rate compared with those receiving more standard therapy.<sup>8</sup> However, studies assessing benefits in survival outcomes are needed. There are currently multiple clinical trials combining pertuzumab with trastuzumab with agents such as paclitaxel and vinorelbine or other investigational agents in patients with locally advanced or metastatic disease.<sup>9-12</sup> 

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## Meet Your HOPA Team

### Kristin Pulatie, Health Policy and Advocacy Manager



**Q. What is your role with HOPA? What are some of the specific things you do on a daily basis for the association?**

A. As health policy and advocacy manager, I work closely with the Health Policy Committee and our consultants at Drinker Biddle & Reath to advance HOPA's health policy agenda. Daily

activities might include researching legislation related to hematology/oncology pharmacy, keeping up to date with policy developments in Washington, DC, and working with the newly formed health policy workgroups on projects related to the agenda.

**Q. How long have you been involved in association work? With which other associations have you worked?**

A. I served on the board of directors for an adolescent health organization (Illinois Caucus for Adolescent Health [ICAH]) for about 18 months before coming to Association Management Center (AMC).

**Q. How did you get your start working with associations?**

A. I received a call for board members for ICAH while in graduate school and was interested in supporting the mission of the organization. I got my start with AMC while looking for policy and advocacy positions focused on health care.

**Q. Where did you grow up?**

A. I grew up in Paradise Valley, AZ, but left to attend college in Boulder, CO, at the University of Colorado. I was a psychology major, and my favorite part of school was traveling abroad with the Semester at Sea program. And skiing. I went skiing a lot.

**Q. What is your favorite thing to do in your spare time?**

A. In the summer and fall I train for triathlons and marathons. In the winter I love to ski. I attend lots of concerts and music festivals and am always up for traveling to see my favorite musicians. I also love to cook and try new activities; my most recent adventure was trapeze lessons. I'm a huge fan of both college football (Go Buffs!) and professional hockey (Go Blackhawks!).

**Q. What is your favorite aspect of working with associations and members?**

A. I enjoy experiencing the enthusiasm of volunteers and working with them to make their organization successful.

**Q. What aspect of working with HOPA is most exciting for you? What are you looking forward to accomplishing this year with HOPA?**

A. HOPA is quickly making progress on health policy agenda action items; it is exciting to see the enthusiasm and passion displayed by committee members. I look forward to reaching out to HOPA members to let them know more about our advocacy activities and hopefully create even greater interest in participating in health policy.

### Molly Pierce, Educational Program Manager



**Q. What is your role with HOPA? What are some of the specific things you do on a daily basis for the association?**

A. My role is to plan and implement all of HOPA's live programming. On a daily basis I work with committee members to develop the annual conference, commercially supported symposia, and preconference and BCOP sessions.

**Q. How long have you been involved in association work? With which other associations have you worked?**

A. I have been involved in association work for 5 years. I previously worked with the American Academy of Dermatology (AAD), American Orthopaedic Society for Sports Medicine, and *Journal of Drugs in Dermatology*.

**Q. How did you get your start working with associations?**

A. My first job out of college was working as the education coordinator for AAD. After that, I couldn't imagine not working for an association!

**Q. Where did you grow up?**

A. I grew up in Rockford, IL, and went to Northern Illinois University, where I graduated with my bachelor of science in corporate communications. I am currently pursuing my master's of education degree in adult and higher education with an emphasis on physician learning in the conference environment.

**Q. What is your favorite thing to do in your spare time?**

A. I'm an avid sand volleyball player, guitarist, and singer. I am typically doing one of those three things on a daily basis.

**Q. What is your favorite aspect of working with associations and members?**

A. I enjoy building relationships with members and volunteers. Being able to see each member's passion for what they do and then developing ways to convey that passion through education are my favorite aspects of the job.

**Q. What aspect of working with HOPA is most exciting for you? What are you looking forward to accomplishing this year with HOPA?**

A. To me, what is most exciting is learning more about the world of pharmacy. I'm eager to learn about our pharmacists and their practices and to implement their ideas and passion into HOPA's annual conference. 