Hematology/Oncology Pharmacy Association

HOPA News

Volume 9, Issue 2

Collaborative Practice Agreements in Oncology: The Future Is Bright

John M. Valgus, PharmD BCOP CPP
Hematology/Oncology Clinical Pharmacist Practitioner
University of North Carolina Hospitals and Clinics, Chapel Hill, NC

Collaborative drug therapy management (CDTM) is a concept that has existed for decades; however, it has not been universally implemented or utilized across pharmacy practice. In 1997 the American College of Clinical Pharmacy (ACCP) released its initial position statement on CDTM by the pharmacist.[1]

The ACCP defines *CDTM* as "a collaborative practice model or agreement between one or more physicians and pharmacists wherein qualified pharmacists working within the context of a defined protocol are permitted to assume professional responsibility for performing patient assessments; ordering drug therapy-related laboratory tests; administering drugs; and selecting, initiating, monitoring, continuing, and adjusting drug regimens."[2] Forty-seven states have legislation in place that allows pharmacists to engage in CDTM; Alabama, Oklahoma, and Maine currently do not have such legislation.

Several states designate pharmacists as midlevel practitioners. This typically entails advanced training and requires the pharmacist to enter into a collaborative practice agreement (CPA). In North Carolina, for example, under the Clinical Pharmacist Practitioner Act of 2000, licensed pharmacists approved by the Board of Pharmacy and the Board of Medicine may enter into CDTM with a physician under a written agreement. These pharmacists may obtain National Provider Identifier (NPI) and Drug Enforcement Administration (DEA) numbers for prescribing authority. New Mexico and Montana have similar legislation; other states that allow pharmacists to obtain a DEA number include California, Minnesota, Massachusetts, North Dakota, and Washington.[3] Despite laws allowing pharmacists to enter into CPAs with physicians, the scope of this agreement varies widely by state and practice setting.

A study conducted by Thomas and colleagues attempted to describe CDTM patterns within the hospital pharmacy.[4] In a survey sent to 1,000 hospitals within the United States, approximately one-half of the 318 respondents affirmed that pharmacists are engaged in CDTM at their institutions. According to the study, hospitals with more than 100 beds or that are located in a city with a population of greater than 10,000 people correlate with an institution providing CDTM. The majority of hospitals use written protocols for CDTM, with infectious disease, coagulation, and parenteral nutrition being the

Contents

most common services defined by CPAs. Study-identified activities involving pharmacists include adjusting drug strength, ordering lab tests, and changing drug administration frequency. However, less than one-half of protocols allow pharmacists to initiate or discontinue drug therapy.

In the ambulatory care setting, a survey of certified pharmacist practitioners (CPPs) in North Carolina and pharmacist clinicians (PCs) in New Mexico showed that approximately 80% of institutions in these states make use of their status as an advanced practitioner.[5] In these two states, the practice setting for CPPs and PCs are widely represented: one-third are in community settings, one-third are in institutional settings, and one-third are in "other" settings (which includes ambulatory clinics). More than half of the respondents indicated that diabetes, coagulation and lipid management, and hypertension were the most common disease states managed. Other areas of practice included asthma and chronic obstructive pulmonary disease, pain, heart failure, and smoking cessation. Respondents stated that the majority of activities within their practice included patient consultation, teaching, administration and management, and medication review. Despite the fact that pharmacists in these states have the ability to obtain NPI or DEA numbers, only one-third of respondents have prescribing authority outlined in their protocols.

Atayee and colleagues describe a pilot program that integrated a pharmacist practitioner into an ambulatory setting.[6] A palliative care pharmacist is integrated into the Doris A. Howell Service at the University of California San Diego Moores Cancer Center. Through a CPA, the palliative care pharmacist is permitted to manage nausea, vomiting, pain, and drug side effects in addition to assessing patients and identifying or resolving drug-related problems. The pharmacist has prescribing authority to initiate or modify treatment plans as permitted by the CPA. Ninety-three percent of interventions in this palliative care setting relate to pain management. The authors report that within about 10 months 29 new patient consults and 114 patient clinic visits were conducted by the palliative care pharmacist. Challenges to implementing the palliative care pharmacist's services include quantifying the pharmacist's activities, educating staff and patients about the service, and receiving funding.

A recent report of a collaborative practice model demonstrated a pharmacist-led interdisciplinary oncology supportive care team. The practice used evidence-based treatment algorithms for commonly seen symptoms such as pain, nausea, vomiting, and constipation. The pharmacist was board certified in oncology, and the supervising physician was board certified in both medical oncology and hospice and palliative medicine. The third member of the team was an advanced practice nurse. The team provided a consult service throughout the week in the various oncology clinics, where the pharmacist and nurse traveled to the patient at scheduled clinic visits. It also consisted of a once-per-week clinic during which all three practitioners were present. The team consulted on 89 patients, which included 292 patient-provider encounters. A large variety of cancer types, including most solid and hematologic malignancies, were represented in the patient consultations. The team demonstrated improvements in symptom scores for pain, nausea, and constipation between the first and second visits. The pharmacist was involved in 67% of the visits, and the physician was involved in 42%. During that time, the pharmacist made 186 interventions and wrote 136 prescriptions. The most common recommendations made were the addition of a new supportive care medication and medication dosage adjustments. Other recommendations included refilling prescriptions and discontinuing inappropriate supportive care medications. This program, utilizing CPAs between a pharmacist and a physician, is a clear example of how this model can be used to extend services provided in the oncology setting and improve the care of cancer patients. This intervention reduced the time burden of the physician by allowing the pharmacist to conduct initial screenings and follow-up visits and managing needed prescriptions for the patient.[7,8]

The collaborative practice agreement in the bone marrow transplant (BMT) clinic at the University of North Carolina has been in place for approximately 18 months. The BMT clinic employs seven physicians, three physician extenders, five coordinators, and nine nurses. Initially the CPA practice was set up in a unique fashion; instead of aligning with a single provider, the agreement listed all seven practicing BMT physicians. When determining the best protocols to implement, the approach was to identify "low hanging fruit" (i.e., activities that a pharmacist could reasonably perform that providers would readily accept and incorporate into practice). The first three identified activities were posttransplant immunizations for vaccine-preventable diseases, chemotherapy counseling for chemomobilization, and postdischarge pharmacy assessment and medication reconciliation. During the the first 6 months of the program, the pharmacist had 290 patient encounters and was able to bill for services for 58% of these patients. Since initiation of this service, pharmacy services have been readily incorporated into the care of nearly all patients in the outpatient setting of the stem cell transplant (SCT) program. In addition to the above activities, the CPP in the SCT clinic now provides preadmission counseling to all allogeneic SCT recipients; manages posttransplant anticoagulation, diabetes, pain, and immunosuppression; and is involved with the development of algorithms and research protocols for the management of cytomegaloviris and graft-versus-host disease and use of plerixafor. On average, the CPP in the outpatient SCT clinic sees approximately 20 patients in face-to-face appointments and provides consultative recommendations and assistance for an additional 20–30 patients per week. We are currently evaluating the pharmacist interventions on the BMT inpatient services and ambulatory clinics, looking at how the interventions affect patients, providers, and nursing staff and determining the perceived value of the pharmacists' clinical activities by these same groups. Data from these evaluations are expected to be available within the next several months.

These examples demonstrate the diverse opportunities for oncology pharmacist–based CPAs. A recent U.S. Public Health Service Report positively describes the role of the pharmacist in a team-based approach to health care.[9] The Surgeon General endorses this report, which may improve the visibility of pharmacist services. In the era of healthcare reform, continued implementation and documentation of pharmacist-based services can only help overcome barriers to providing team-based services through CPAs. The ultimate hope is to influence future legislation that recognizes pharmacists as providers.

Several barriers limit the implementation of pharmacy-based services under CPAs. The majority of the examples above identify funding as a significant barrier to establishing pharmacy-based services, especially during the start-up phase. It is important for new and existing oncology programs using the CPA model to identify priorities that will demonstrate the positive impact pharmacists may have on healthcare delivery. Publications describing the details of such practices, and demonstrating the impact of pharmacist CPAs on clinical outcomes and patient satisfaction, as well as mechanisms for revenue generation and cost reduction, will encourage institutions to support such services and activities in the future. The aforementioned CPA-related services mentioned above have allowed for increased access to care, improved medication utilization, and improved oncologist availability to see new patients. It is imperative that interventions are documented to justify the pharmacist-based service and secure more permanent funding to sustain this service.[4-8]

State-specific legislation that restricts the types of CPAs in which pharmacists may enter is another barrier. Fortunately, healthcare organizations and the federal government, seeking to meet ever-growing healthcare demands, have shown increasing support for the model. A survey conducted by the American Society for Clinical Oncology (ASCO) forecasts a shortage of oncologists by 2020.[10] The survey explains that an aging population, an increase in cancer survivorship, and an increasing prevalence in malignancies all contribute to a demand for oncologists that will likely not be met with an adequate supply. ASCO describes several actions to mitigate this projected shortage such as utilizing nurse practitioners and physician assistants to help manage clinic visits. Noticeably absent from this proposed solution were pharmacists. A recent editorial by Sessions and colleagues highlights how oncology pharmacists working within CPAs can help alleviate the impact of the oncologist shortage.[11] Clearly, the examples of pharmacist-based services mentioned in this article demonstrate that pharmacists are qualified practitioners to help meet this demand.

Including pharmacists within a CPA is a growing trend that could potentially improve the access and quality of care for patients. A few examples of such practices in oncology have been published that demonstrate the breadth of activities a pharmacist can manage within this setting. Future strategies for implementing CPAs should focus on developing prioritized goals that demonstrate the value an oncology pharmacist brings to the healthcare team in this expanded role. Only then will organizations and institutions recognize the value and potential of oncology pharmacists practicing within CPAs.

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Controversies in Oncology: Bevacizumab for the Treatment of Metastatic Breast Cancer

Chad Barnett, PharmD BCOP
Clinical Pharmacy Specialist, Breast Oncology
MD Anderson Cancer Center, Houston, TX

Bevacizumab is a humanized monoclonal antibody targeted against vascular endothelial growth factor (VEGF), a key mediator of angiogenesis, and is used in or under investigation for the treatment of a wide variety of solid tumors.[1] Bevacizumab use in patients with metastatic breast cancer (MBC) is controversial for many reasons, including (but not limited to) the use of surrogate endpoints for determination of overall survival (OS) in advanced cancer, the appropriate risk/benefit analysis of new therapeutic agents, and the economics associated with emerging oncologic therapy. A comprehensive update on the ongoing controversies of bevacizumab in MBC is beyond the scope of this article; however, knowledge of recent events related to U.S. Food and Drug Administration (FDA) approval and the current status of bevacizumab for patients with MBC is crucial to the practicing oncology pharmacist who routinely manages these patients.

Results from an interim analysis of the Eastern Cooperative Oncology Group (ECOG) E2100 trial provided data to support consideration of accelerated approval for bevacizumab in patients with MBC.[2,3] Patients with MBC in the first-line setting (N = 722) were randomized to receive paclitaxel alone (90 mg/m^2 intravenously on days 1, 8, and 15 of a 28-day cycle) or in combination with bevacizumab (10 mg/kg intravenously every 2 weeks). Response rates (37% versus 21%, $p < .001$) and progression-free survival (PFS; 11.8 months versus 5.9 months, hazard ratio [HR] = 0.60, $p < .001$) were superior in patients who received paclitaxel in combination with bevacizumab compared to paclitaxel alone, respectively. OS was not significantly different between the two groups (26.7 months versus 25.2 months, HR = 0.88, $p = .16$). Based on these initial results, the Oncology Drug Advisory Committee (ODAC) voted five to four against accelerated approval for bevacizumab in patients with MBC.[4] Despite this recommendation, the FDA granted bevacizumab accelerated approval on February 22, 2008, for patients who had not received prior chemotherapy for HER2-negative MBC based on PFS results from the E2100 trial. The FDA required that the manufacturer (Genentech) "conduct adequate and well-controlled studies to further define the degree of clinical benefit to patients" to confirm or refute these results.

Two additional phase 3 trials were designed to validate the results of the E2100 study in patients with MBC. Newly diagnosed patients with MBC (N = 736) in the AVADO (avastin and docetaxel) trial were randomized to receive docetaxel plus bevacizumab or placebo (both administered every 3 weeks).[5] The Regimens in Vevacizumab for Breast Oncology (RIBBON-1) trial enrolled 1,237 patients and evaluated bevacizumab in addition to first-line chemotherapy, which included anthracycline-based regimens (AC, FEC, CAF, or EC), taxanes (docetaxel or nab-paclitaxel), or capecitabine.[6] Statistically significant improvements in response rates and PFS were achieved in both trials with the addition of bevacizumab to chemotherapy, although the magnitude of benefit was lower than expected compared with results from the E2100 trial (PFS improvement of 10.1 months versus 8.2 months in the bevacizumab 15-mg/kg arm of the AVADO trial, 9.2 months versus 8.0 months in the anthracycline and taxane arm of the RIBBON-1 trial, and 8.6 months versus 5.7 months in the capecitabine arm of the RIBBON-1 trial). Neither trial demonstrated an improvement in OS or quality of life with the addition of bevacizumab to first-line chemotherapy in patients with MBC. A meta-analysis of these three trials demonstrated an improvement in median PFS with bevacizumab and chemotherapy compared with chemotherapy alone (9.2 months versus 6.7 months, HR = 0.64, $p < .0001$) but no difference in OS.[7]

On July 20, 2010, the ODAC panel met again to discuss the conversion of bevacizumab for treatment of first-line MBC from accelerated to regular approval and to consider expansion of approval to include use of bevacizumab with docetaxel-, capecitabine-, or anthracycline-based chemotherapy in the first-line setting based on data from the RIBBON-1 clinical trial.[8] The panel voted 12 to 1 to remove the breast cancer indication from the bevacizumab label. The FDA revoked the breast cancer indication for bevacizumab on November 18, 2011, after concluding it has not been shown to be safe and effective for that use.[9] Bevacizumab is still included as an acceptable therapeutic agent in the *National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for Breast Cancer*, but the guidelines' authors add that "the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel."[10]

Goals of treatment for MBC are palliative in nature, making toxicities related to drug therapy especially important when considering treatment options. Toxicity concerns were central to the FDA's decision to revoke bevacizumab's breast cancer indication. In the E2100 trial, patients who received bevacizumab experienced significantly increased rates of grade 3–4 infection, fatigue, sensory neuropathy, hypertension, cerebrovascular ischemia, headache, and proteinuria.[2] The Avastin Therapy for Advanced Breast Cancer (ATHENA) trial was an open-label, single-arm, international study conducted to provide additional efficacy and safety data for bevacizumab in the first-line setting.[11] Grade 3 or higher toxicities included febrile neutropenia (5.3%), hypertension (4.4%), thromboembolism (3.4%), proteinuria (1.7%), and hemorrhage (1.4%). Bevacizumab was permanently discontinued due to toxicity in 18.9% of patients.

Use of surrogate endpoints for OS in patients with MBC, such as PFS, has been widely debated. Survival is the most unambiguous clinical endpoint because it is the net effect of both drug efficacy and toxicity. Survival is usually the preferred endpoint of the FDA, although the FDA has accepted endpoints such as PFS in some cases if the magnitude of benefit is large and toxicities are acceptable.[12] A more detailed review of this debate has been described elsewhere.[13]

Economic considerations of bevacizumab use in patients with MBC have also been a subject of debate. The average wholesale price for a 400-mg vial of bevacizumab is $2,801.52.[14] The cost for 1 year of life saved with a course of bevacizumab has been estimated at $496,072.[15] Off-label use of bevacizumab in patients with MBC is allowed, however, insurers may not cover the associated drug costs. As previously mentioned, bevacizumab is still included as an acceptable therapeutic agent in the *NCCN Clinical Practice Guidelines in Oncology for Breast Cancer,*[10] which may provide a rationale for insurance coverage.

Identifying breast cancer patients who derive the most benefit from bevacizumab has been difficult. Heavily pretreated patients may not benefit as much from bevacizumab compared with untreated patients. In a randomized clinical trial that evaluated bevacizumab administered every 3 weeks in combination with capecitabine in women who had failed both anthracycline- and taxane-containing regimens (*N* = 462), the addition of bevacizumab significantly improved the overall response rate, but median PFS and OS were not significantly different from patients who received capecitabine alone.[16] Some researchers have proposed the evaluation of reliable biomarkers to predict the likelihood of response to bevacizumab. Unfortunately, no such biomarker currently exists for the selection of appropriate candidates for bevacizumab in patients with MBC.

The discussion of bevacizumab for patients with breast cancer has been reignited with the publication of two separate studies of bevacizumab in combination with neoadjuvant chemotherapy in women with HER2-negative stage 1–3 breast cancer. Results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B40 and GeparQuinto (GBG44) trials were published in the *New England Journal of Medicine* in January 2012.[17,18] These trials also included a surrogate endpoint, pathological complete response (pCR), as the primary endpoint of these studies, although the definitions differed (NSABP B40, absence of residual tumor in the breast; GBG44, absence of residual tumor in the breast and lymph nodes). Both studies showed a significant improvement in the rates of pCR with the addition of bevacizumab to neoadjuvant chemotherapy. OS data from these clinical trials are not yet mature. Investigators from both study groups are analyzing biomarkers that they hope will help identify patients who receive the most benefit from bevacizumab. Although intriguing, these studies do not currently provide a new standard of care for patients with nonmetastatic breast cancer undergoing treatment with neoadjuvant chemotherapy. Further follow-up regarding breast cancer recurrence and survival from these and other clinical trials are anxiously awaited.

In summary, the use of bevacizumab in patients with MBC continues to be controversial, with opposing views persisting in the medical literature and lay press. Although the FDA revoked the breast cancer indication for bevacizumab, the *NCCN Clinical Practice Guidelines in Oncology for Breast Cancer* still include bevacizumab as an option. Active debate regarding the optimal use of bevacizumab in patients with breast cancer is ongoing, and there continues to be hope that we can accurately identify patients who derive the most benefit from this agent in the future and spare unnecessary toxicity for those who will not benefit.

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Continued on page 6

Controversies in Oncology: Bevacizumab for the Treatment of Metastatic Breast Cancer *(continued from page 5)*

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Lipodox Importation Approved by FDA

Dear HOPA members,

In response to the prolonged critical shortage of Doxil® (doxorubicin hydrochloride liposome injection), the U.S. Food and Drug Administration (FDA) has allowed (since January 2012) the temporary importation and distribution of Sun Pharma Global's Lipodox™ (doxorubicin hydrochloride liposome injection) in the United States by Sun Pharma Global FZE and its authorized distributor, Caraco Pharmaceutical Laboratories Ltd. The FDA's current authorization to import Lipodox™ is not expected to satisfy the full demand for the drug for all institutions; allotments may only include a limited number of vials to be distributed on a monthly basis to requesting institutions. The importation or distribution of this drug in the United States by any other entity is not allowed. Sun Pharma Global's Lipodox™ remains unapproved by FDA for marketing in the United States.

On May 9, 2012, Janssen Products, LP, announced it has reopened enrollment in the DOXIL® C.A.R.E.S. Physician Access Program (for more information, visit www.doxil.com/doxil-supply-shortage). It is unknown whether reenrollment will fully satisfy the demand for the drug for all institutions; for this reason the Lipodox™ supply will also remain available.

Current information about the imported drug is posted on the FDA drug shortage Web page (www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm). This information has also been added to the HOPA website for members to review. There are several notable differences between the Doxil® and Lipodox™ dosage forms (**Table 1**). Prescribers, pharmacists, and other healthcare professionals should be aware of these differences, including indications for use, pharmacokinetics, adverse effects, and dosing adjustments.

To obtain Lipodox™, contact the Sun Pharma shortage response team by phone (888.835.2237) or fax (800.980.2237).

Sincerely,

HOPA Legislative Affairs Committee

Table 1. Differences in Dosage Forms for Doxil and Lipodox

	Doxil® (Janssen Products, LP)	Lipodox™ (Sun Pharma)
Indications	Ovarian cancer[a] AIDS-related Kaposi's sarcoma[b] Multiple myeloma[c]	Metastatic breast cancer[d] Refractory ovarian cancer[e] AIDS-related Kaposi's sarcoma[f]
Half-life	55 hrs	55 hrs
Adverse effects	Infusion reactions Derm: hand-foot syndrome, radiation recall, rash GI: anorexia, constipation, diarrhea, nausea, stomatitis, vomiting, Heme: anemia, neutropenia, thrombocytopenia Neuro-psych: asthenia, fatigue, fever	Infusion reactions Derm: hand-foot syndrome, rash GI: anorexia, diarrhea, abdominal pain, dyspepsia, stomatitis Heme: anemia, neutropenia, thrombocytopenia Neuro-psych: asthenia, fatigue, fever
Dose adjustments	*Based on bilirubin* 1.2–3 mg/dL: give 50% of normal dose >3 mg/dL: give 25% of normal dose	*Based on bilirubin* 1.2–3 mg/dL: reduce first dose by 25% >3 mg/dL: reduce first dose by 50% Principal investigator suggests increases in dosing adjustments based on tolerance to the drug with elevated bilirubin or liver enzymes

Note. Slight differences in dose adjustments based on hematology, palmar-plantar erythrodysesthesia, and stomatitis exist between the two drugs.

[a] *In disease progression or recurrence after platinum-based chemotherapy*

[b] *After failure of prior systemic therapy or intolerance to such therapy*

[c] *In combination with bortezomib in patients who have not previously received bortezomib and have received at least one prior therapy*

[d] *As monotherapy where there is an increased cardiac risk*

[e] *Refractory to both paclitaxel- and platinum-based chemotherapy regimens;* refractory disease *is defined as disease that has progressed while on treatment or within 6 months of completing treatment.*

[f] *In patients with extensive mucocutaneous or visceral disease that has progressed on prior combination therapy (consisting of two of the following agents: a vinca alkaloid, bleomycin and standard doxorubicin or another anthracycline) or in patients who are intolerant to such therapy.*

Imatinib Mesylate for Adjuvant Therapy of GIST: A New FDA Approval

Karen M. Fancher, PharmD BCOP
Clinical Pharmacy Specialist
West Penn Allegheny Oncology Network, Pittsburgh, PA

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract, with an annual incidence of approximately 10 cases per million.[1] They are usually found in the stomach or small intestine but can occur at any site in the GI tract.[1,2] Common presenting signs include early satiety, abdominal discomfort, intraperitoneal hemorrhage, GI bleeding, or fatigue related to anemia. Surgery is the primary treatment of choice for patients with localized or potentially resectable lesions, with complete resection possible in 85% of cases. However, 50% of these patients will recur or develop metastases, and the 5-year survival rate of these patients is approximately 50%.[1,2] GISTs are universally resistant to conventional chemotherapy.[2] Up to 95% of GISTs harbor an activating mutation in the KIT oncogene, and a small portion have mutations in the platelet-derived growth factor receptor-alpha (PDGFRA),[1-3] both of which are considered early events in the oncogenesis of a GIST.[3]

Imatinib mesylate was originally designed as a specific inhibitor of the Bcr-Abl tyrosine kinase for the treatment of chronic myelogenous leukemia. In addition, imatinib is also a potent inhibitor of the tyrosine kinase activities of KIT and PDGFRA.[3] The U.S. Food and Drug Administration (FDA) granted accelerated approval of imatinib for the treatment of patients with KIT-positive unresectable or metastatic malignant GISTs in February 2002, and regular approval was granted for this indication in 2008.[2,4,5] Imatinib was also granted accelerated approval for use in postoperative treatment of KIT-positive GISTs in December 2008[2,6]; however, the appropriate duration of therapy remained unclear because most patients have disease progression upon discontinuing therapy.[1,6]

A recently completed trial examined the use of extended-duration imatinib therapy in this population. Four hundred high-risk patients with KIT-positive GIST participated in a randomized, open-label, phase 3 study conducted in 24 hospitals in Scandanavia. After removal of the tumor during surgery, patients were stratified and assigned in a 1-to-1 ratio to treatment with imatinib 400 mg by mouth (PO) daily for 12 months or to the same dose of imatinib for 36 months. The primary objective was recurrence-free survival (RFS). Secondary objectives included overall survival (OS), treatment safety, and GIST-specific survival, defined as the time period from the date of randomization to the date of death considered to be caused by GIST. At a median follow up of 54 months, RFS was longer in the 36-month group compared with the 12-month group (5-year RFS, 65.6% versus 47.9%; hazard ratio [HR] = 0.46; 95% CI = 0.32–0.65; $p < .001$). OS was also longer in the 36-month group (5-year survival, 92% versus 81.7%; HR = 0.45; 95% CI = 0.22–0.89; $p = .02$). Survival specific to GIST tended to favor the 3-year group, with a 5-year GIST-specific survival of 95.1% versus 88.5% (HR = 0.46; 95% CI = 0.19–1.14; $p = .09$). Most interestingly, no significant difference in the hazard of GIST recurrence or death was noted between the two groups during the first 12 months after randomization or after 36 months of randomization, but a substantial difference emerged during 12 to 24 months after randomization and 24 to 36 months after randomization (HR = 0.26, 95% CI = 0.13–0.53 and HR = 0.17, 95% CI = 0.07–0.39, respectively). This finding suggests that these differences occurred only when patients were actively taking the drug.[1]

In an exploratory subgroup analysis, patients with GIST with KIT exon 11 mutation benefitted from longer imatinib administration (HR = 0.35, 95% CI = 0.22–0.56). Conversely, no significant improvement during 12 months of imatinib was found in the subsets of patients with KIT exon 9 mutation, PDGFRA mutation, or no genetic mutations; however, the numbers of patients in these subgroups were small.[1]

Imatinib was generally well-tolerated, but nearly all patients reported at least one mild adverse effect. The most frequently reported grade 3 or 4 adverse events were leukopenia (5.1%), diarrhea (2.5%), and nausea (2%). A larger proportion of patients in the 36-month group discontinued imatinib for a reason other than GIST recurrence (25.8% versus 12.6%).[1]

Based on the results of this study, the FDA granted regular approval of imatinib mesylate for the treatment of adults who have undergone surgical removal of KIT-positive GIST.[1,4] The optimal duration of treatment remains unknown, and further studies that evaluate extended treatment, safety, and novel combination therapy are still warranted.

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American Society for Blood and Marrow Transplantation: 2012 BMT Tandem Meeting Highlights

Kaci Wilhelm, PharmD BCOP
Clinical Pharmacy Specialist Blood and Marrow Transplantation
The University of Texas MD Anderson Cancer Center, Houston, TX

The 2012 American Society for Blood and Marrow Transplantation (ASBMT) BMT Tandem Meeting took place in San Diego, CA, February 1–5, 2012. More than 100 abstracts were selected for oral presentations. Below are selected noteworthy abstracts from the 2012 meeting. All accepted abstracts were published in the February issue of *Biology of Blood and Marrow Transplantation* (Vol. 18, No. 2, Suppl. 2).

Abstract 5: *CMX001 for Prevention and Control of CMV Infection in CMV-Seropositive Allogeneic Stem-Cell Transplant Recipients: A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Trial of Safety, Tolerability, and Antiviral Activity*

CMX001 is an oral liposomal cidofovir conjugate with in vitro activity against herpes viruses, adenoviruses, polyomaviruses, and orthopoxviruses. CMX001 was evaluated for safety and efficacy in this phase 2 multicenter, randomized, placebo-controlled, double-blind, dose-escalation study. This study evaluated 230 adult allogeneic hematopoietic stem cell transplant (AlloHSCT) recipients who were cytomegalovirus (CMV)-seropositive. Patients were stratified post-AlloHSCT according to acute graft-versus-host disease requiring corticosteroid therapy or presence of CMV viremia. There were five dose escalation cohorts, ranging from 40 mg weekly to 200 mg twice weekly. Treatment duration was 9 to 11 weeks. The composite endpoint was defined as CMV disease or appearance or progression of CMV viremia. Patients meeting this definition discontinued the study drug and received anti-CMV treatment as clinically indicated.

In the higher dose cohorts (≥200 mg/week), CMX001 demonstrated a reduction in appearance or progression of CMV viremia or disease by day 100 post-AlloHSCT. Diarrhea was dose limiting in the highest dose cohort (200 mg twice weekly). No significant changes in renal or graft function were noted.

The authors concluded that CMX001 has potential as a prophylactic agent against CMV in this population. Compared to currently available anti-CMV agents, advantages of CMX001 include oral availability and minimal effects on both renal and graft function.

Studies evaluating the efficacy of CMX001 against adenovirus in immunocompromised patients are underway.

Abstract 12: *Comparison of Gemcitabine, Busulfan, and Melphalan (Gem/Bu/Mel) with BEAM and Busulfan/Melphalan (Bu/Mel) in Concurrent Cohorts of Refractory Hodgkin's Lymphoma Patients Receiving an Autologous Stem-Cell Transplant*

Patients with Hodgkin's lymphoma with high-risk relapse or primary refractory disease have poor outcomes with BEAM regimen followed by autologous stem cell transplant (AutoHSCT). The Gem/Bu/Mel regimen was designed to incorporate the DNA damage repair inhibition of gemcitabine with the alkylating agents busulfan and melphalan. This regimen was evaluated in a dose-escalation trial in patients with refractory Hodgkin's lymphoma. Refractory disease was defined as primary induction failure, CR1 lasting less than 6 months, or greater than one relapse.

The maximum tolerated dose of gemcitabine was 2,775 mg/m^2/day intravenously (IV) on days -8 and -3 administered; it was administered as a 75-mg/m^2 bolus, followed by 2,700 mg/m^2 infused at a fixed dose rate of 10 mg/m^2/min. Busulfan was administered IV in four daily doses on days -8 through -5 to a daily target area under the curve (AUC) of 4,000 mmol/min. Several days prior to initiation of the high-dose regimen, a busulfan test dose (32 mg/m^2) was administered to facilitate pharmacokinetic-directed dosing of the four therapeutic doses. Melphalan was administered at 60 mg/m^2 IV on day -3 and day -2.

Gem/Bu/Mel was compared with concurrent cohorts of patients with refractory Hodgkin's lymphoma receiving either BEAM or Bu/Mel. A total of 209 patients were evaluated. The Gem/Bu/Mel group had significantly more patients with poor prognostic features such as primary induction failure, bulky tumor at relapse, extranodal disease at relapse, PET+, and progressive disease at time of AutoHSCT. Overall and complete response rates were 93% and 81% for Gem/Bu/Mel, 93% and 66% for BEAM, and 64% and 64% for Bu/Mel, respectively. Patients in the Gem/Bu/Mel group experienced prolonged event-free survival (EFS; 63% versus 42% versus 38%, p = .002) and overall

survival (OS; 85% versus 63% versus 62%, $p = .02$) despite worse prognostic features. Median follow up was 16 months in the Gem/Bu/Mel group, 17 months in BEAM group, and 36 months in the Bu/Mel group.

The Gem/Bu/Mel regimen demonstrated promising results in patients with refractory Hodgkin's lymphoma with significant improvement in both EFS and OS. A randomized trial to confirm these benefits is warranted.

This regimen was also evaluated in patients with poor-risk or refractory non-Hodgkin's lymphoma and demonstrated promising response rates (see **Abstract 11**).

Abstract 16: *Phase II Pilot Study of Imatinib Mesylate for the Treatment of Severe Sclerotic Skin Chronic Graft-Versus-Host Disease (ScGVHD)*

Imatinib mesylate is a tyrosine kinase inhibitor that has been approved by the U.S. Food and Drug Administration for chronic myeloid leukemia. It also has activity against platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β), which have been implicated in the development of severe sclerotic skin chronic graft-versus-host disease (ScGvHD).

Twenty patients were enrolled in this phase 2 pilot study. Patients had ScGvHD that limited range of motion by >25% in at least one joint. Initially, imatinib was started at 400 mg/day, but because of toxicity the dose was subsequently changed to 100 mg/day with escalation to 200 mg/day after 1 month. The primary efficacy endpoint was assessed at 6 months. This endpoint was defined as percentage improvement (range of motion) compared with baseline at 1–3 target joints. Partial response was >25% improvement, progressive disease was >25% decrease or >1 steroid pulse per 3-month period, and responses not meeting these definitions were classified as stable disease.

Of the 20 enrolled patients, 16 were eligible for evaluation. Five patients experienced partial response, seven had stable disease, and two patients had progressive disease. Of the patients with improvement, the average gain in range of motion was 31%. Adverse effects were frequent and included hypophosphatemia, gastrointestinal upset, fatigue, muscle cramping, tinnitus, and pain. Two patients required hospitalization for pulmonary edema.

Imatinib mesylate for 6 months improved range of motion in the majority of patients. Due to toxicity, the starting dose was modified to 100 mg/day with escalation to 200 mg/day after 1 month. Even with this dose reduction, adverse effects were a significant limitation of imatinib use in this population.

International Medication Safety Self-Assessment for Oncology Practice

Philip E. Johnson, MS RPh; Carole R. Chambers, MBA BSc; Allen J. Vaida, PharmD FASHP; Julie Greenall, RPh BScPhm FISMPC MHSc; Michael R. Cohen, RPh MS ScD

A comprehensive survey of compliance with oncology medication safe practice standards was conducted in 2008.[1] Responses from 377 participants representing 34 countries demonstrated a wide variance in adherence to established standards and best practices (22.3%–98.3%). Since then, new standards have been published by several organizations, and new best practices have been promoted through publications and presentations. There are currently multiple standards, and it is clear from medication error reports that many important standards are not fully understood and compliance is not optimal.

The Institute for Safe Medication Practices (ISMP), ISMP Canada, and the International Society of Oncology Pharmacy Practitioners (ISOPP) launched the 2012 ISMP International Medication Safety Self-Assessment for Oncology, a self-assessment tool designed to help hospitals and ambulatory cancer centers throughout the world evaluate oncology medication safety. This tool will establish an international baseline for safe medication practices related to oncology practice and will identify areas for improvement.

A multidisciplinary team of 29 international experts evaluated published world standards, which resulted in a consensus opinion on current best practices. This was the basis for the development of the oncology self-assessment tool. The assessment items are divided into the key elements (domains) that most significantly influence a safe medication use process. The key elements include (1) patient information; (2) drug information; (3) communication of drug orders and other drug information; (4) drug labeling, packaging, and nomenclature; (5) drug standardization, storage, and distribution; (6) medication device acquisition, use, and monitoring; (7) environmental factors, workflow, and staffing patterns; (8) staff competency and education; (9) patient education; and (10) quality processes and risk management.

As with ISMP's previous self-assessments, healthcare organizations will be asked to convene multidisciplinary teams to complete the self-assessment tool and submit data confidentially through a secure Web-based form. Respondents will then be able to compare their results with aggregate data from other demographically similar organizations. The assessment will be available on the websites of ISMP (www.ismp.org), ISMP Canada (www.ismp-canada.org), and ISOPP (www.isopp.org), as well as other organizations that will help support its use. To access this important tool, visit www.ismp.org or https://mmsa.ismp-canada.org/oncology.

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Board Update

R. Donald Harvey, PharmD BCPS BCOP FCCP, HOPA Past President

The Evolution of HOPA

As we transition leadership for 2012–2013, we should take time to assess organizational health, direction, and accomplishments. Our investments in the fundamentals of the strategic plan—advocacy, education, and practice standards—continue to augment the role of pharmacists in the care of people affected by cancer. From increased exposure in Washington to a publication on a drug shortage survey to expanded educational opportunities, HOPA continues a trajectory of growth and professional development in areas of importance to members and patients.

The Individual as Member and Ambassador

All of our efforts rely on one common denominator—individual efforts. During the coming months, you will see a transition and growth of the HOPA website to expand the visibility and role of members in advocacy. HOPA has joined a number of coalitions, including the Cancer Leadership Council, the Health Professions and Nursing Education Coalition, the National Coalition for Cancer Research, and the Pain Care Forum. We expect our professional voice to continue growing in volume and importance through these affiliations.

We rely on personal motivation and relationships to open doors for the profession and organization. I urge you to reach beyond your comfort zone and become educated on how to talk to your legislators regarding the issues that directly affect you now and in the future (e.g., reimbursement, shortages, patient access to oral chemotherapy, REMS programs, healthcare reform, biosimilars, and other concerns). Similarly, be an ambassador in your institution for the profession and in other organizations for HOPA. Most importantly, be an advocate for your patients.

The Path to Future Changes in Care

The HOPA Foundation has opened the call for grant proposals. Up to three proposals will be funded, with a total amount of $50,000 available. To mirror HOPA's organizational goals, HOPA research grants are intended to provide support for projects that are likely to result in facilitating the efforts of hematology/oncology pharmacists to optimize the care of individuals affected by cancer. For those who may be intimidated by submitting proposals, there are many members who have expertise in designing, conducting, and reporting research efforts and who would be happy to share their knowledge. Take advantage of those contacts and expand your practice horizons.

The Value of Continuity

Education and networking through the annual conference continues to be a successful enterprise thanks to experienced meeting planning, knowledgeable speakers, and support from our industry partners. This year's conference was no exception; the sessions were well attended and dialogue among members was constant. Make plans to join us in 2013 in Los Angeles for another exceptional conference.

I am thankful to my colleagues for their support during the past year. The future of hematology/oncology pharmacy continues on an upward trajectory thanks to HOPA members and their efforts.

Committee Updates

BCOP Recertification Committee

Ryan Bookout, Chair
Debbie Blamble, Vice Chair

The BCOP Recertification Committee, the BCOP Review Panel, and the 2012 annual conference speakers had a busy couple of months leading up to the HOPA Annual Conference. We were finalizing the six 2012 Oncology Pharmacy Specialty Sessions for BCOP recertification as well as the exam for recertification credit. All of our efforts paid off, and we were pleased to see the sessions presented for the first time at the 2012 HOPA Annual Conference, held in Orlando, FL, in March. We are eagerly awaiting feedback from the conference evaluations to see how we can improve the sessions and continue to meet members' needs. Many thanks to the speakers as well as the members of the committee and review panel for all of their hard work and to make such programming possible.

As a reminder, the topics for the 2012 Oncology Pharmacy Specialty Sessions for BCOP recertification are

- Therapy of T-Cell and Cutaneous Lymphomas: There's More Than Just B Cells—Patrick Kiel, PharmD BCPS BCOP
- Neuroendocrine Tumors: A Focus on Recent Advances in Pharmacotherapy—J. Hoyt Slade III, PharmD BCOP
- Bone Health in the Oncology Population—Chad Barnett, PharmD BCOP
- Treatment Progress for Advanced Non-Small Cell Lung Cancer—Christine Walko, PharmD BCOP
- Trends in Oncology Drug Expenditures and Practical Cost-Management Strategies—James Hoffman, PharmD MS BCPS
- The Emergence of Adolescent and Young Adult Oncology—Kerry Parsons, PharmD BCOP.

The sessions will be offered two more times in 2012 at the following meetings: the American College of Clinical Pharmacy Annual

Meeting in Hollywood, FL, October 21–24, and the American Society of Health-System Pharmacists Midyear Clinical Meeting in Las Vegas, NV, December 2–6. We hope everyone has the opportunity to attend the sessions at one of these meetings. Remember, to receive BCOP recertification continuing education credit, you must attend all 6 hours of programming at the same meeting and successfully pass the associated exam. Partial credit will not be awarded. Any BCOP pharmacist who attends all six sessions should receive an e-mail shortly after the attended meeting with a link to the exam. Please contact HOPA (info@hoparx.org) if you do not receive an e-mail.

The committee leadership would again like to thank the members of the 2011–2012 BCOP Recertification Committee and BCOP Review Panel. We couldn't have done it without you. And we wish the best of luck to the incoming 2012–2013 members.

CPE Accreditation Committee

Carol Balmer, Chair
Jolynn Sessions, Vice Chair

With the generous dedication of the CPE Review Panel, Accreditation Committee, and HOPA staff, nearly 50 presentations were accredited for the HOPA Annual Conference. Accredited sessions included the preconference Boot Camp, all of the full group and breakout sessions for the 3-day annual conference, and four supported symposia.

CPE reviewers are responsible for ensuring that each accredited activity complies fully with Accreditation Council for Pharmacy Education's (ACPE's) standards for accreditation. The review process requires detailed review of the learning objectives, slide sets, active learning plans, and learning assessments. Although the main focus of the CPE review is accreditation related, CPE reviewers also address content-related issues to help ensure that sessions are current, represent standard of care, and are evidence based. Content-related issues are also reviewed concurrently by members of the committees responsible for overseeing each session (Program, Education, or BCOP Recertification Committees). The chair of each responsible committee compiles the comments from all reviewers, shares them with the speakers, and coordinates revisions. Sometimes a second CPE review is required.

Several process changes are being considered by the CPE Accreditation Committee that may help streamline the review process for the 2013 annual conference. One consideration under review is adopting a standardized list of performance verbs for learning objectives for HOPA-accredited CPE activities.

In addition to addressing procedural issues, the CPE Accreditation Committee is also involved in early preparation steps for the upcoming ACPE Self-Study Report. The CPE Review Panel members have completed their primary responsibilities but will continue to serve as CPE reviewers for HOPA home-study activities.

I extend my heartfelt thanks to Jolynn Sessions, vice chair, and to all of the CPE Accreditation Committee and Review Panel members for their dedicated service and generous contributions during the 2011–2012 committee year. Congratulations to Jolynn, who will assume chair responsibilities for 2012–2013. Thank you!

Education Committee

Helen Marshall, Chair
Laura Wiggins, Vice Chair

Many of the committee members of the Education Committee were able to attend the HOPA Annual Conference in Orlando, FL. The Oncology Boot Camp session focused on tyrosine kinase inhibitors was a great way to kick off the meeting with exceptional speakers and fantastic attendance. The committee will begin planning and developing future Boot Camp programming in June. The committee is currently completing its evaluation of the HOPA University website and HotTopics seminars. The chair and vice chair would like to express gratitude for all of the hard work the committee members contributed to the Education Committee this year.

Legislative Affairs Committee

Ali McBride, Chair
Tim Tyler, Vice Chair

The HOPA Legislative Affairs Committee addressed several topics this year that affect clinical and management practices in oncology. The topics include drug shortages, oral chemotherapy issues, and risk evaluation and mitigation strategies (REMS). The HOPA drug shortage survey, written by HOPA Legislative Affairs Committee members, attempted to identify drug safety issues, clinical studies, clinical practices, and costs related to drug shortages. The survey data have been compiled and evaluated, and the outcomes will be released to HOPA members in the near future.

One of the most salient issues affecting our practices is oral chemotherapy. Each year we see an increase in the number of oral oncolytics in the market place and in the research pipeline. Approximately 25% of all new chemotherapy agents will be developed in an oral form. Unfortunately, patients cannot always afford their copays, especially when patients have Medicaid and are forced to deal with the high initial cost of these drugs. Dean Gruber and Sarah Hudson-DiSalle have developed a survey to identify issues facing clinical practitioners regarding oral chemotherapy. The survey will be out shortly and will evaluate how oral chemotherapy treatments affect our members. The results will help inform our legislative agenda.

I laud all of the work of HOPA Legislative Affairs Committee members. Each member provided key pieces of information to the committee to address HOPA members' concerns. I would like to acknowledge James Hoffman for his work on legislative issues affecting oncology pharmacy, which was essential to all of the accomplishments our committee made this year (from drug shortages to oral chemotherapy); Colleen Westendorf for her continued assistance with the HOPA drug shortage survey (especially in light of her ever-growing homework load); Ray Muller for his great discussion and topics development regarding oncology issues and Yankee's baseball; and Phil Johnson for his mentorship when I took on the role of committee chair (thank you, Phil, for your continued support). The last thank you goes out to all of the HOPA members who have voiced their concerns about issues affecting our profession. It was you who we served, and we thank you for all of your work when taking care of patients. The HOPA Legislative Affairs Committee looks forward to new changes

in the upcoming year, including the addition of our new lobbying group Drinker Biddle & Reath and the development of the Health Policy Committee.

Thank you for letting us represent you during these challenging and difficult times—when health care is changing so quickly before our eyes.

Nominations and Awards Committee

Laura Jung, Chair
Jane Pruemer, Vice Chair

Nominations for HOPA awards are now open. Members can nominate other HOPA members for these awards on the HOPA website, www.hoparx.org. The nomination period for the HOPA awards will end October 1, 2012. Board of directors nominations will be open June 28, 2012, through August 2, 2012.

Program Committee

Jill Rhodes, Chair
Larry Buie, Vice Chair

The 2012 HOPA 8th Annual Conference held in Orlando, FL, was a great success! This year several new conference features were debuted, including a practice issue panel, Clinical Pearls sessions, and a call for session proposals. The practice issue panel generated significant attendee discussion about the impact of drug shortages on oncology pharmacy. The Clinical Pearls sessions focused on four real-life conundrums facing pharmacists in everyday clinical practice. In addition, the research task force was very busy on site during the conference reviewing trainee research-in-progress abstracts. We are happy to announce that the HOPA 8th Annual Conference hosted the highest number of poster presentations to date. The Program Committee would like to thank attendees for their valuable responses and evaluations of the annual conference. Membership feedback is integral in the program planning for future events and is greatly appreciated.

Opportunities for continued membership involvement in the upcoming HOPA conference will soon be available. Because the call for session proposals was so successful for the 2012 annual conference program, it is going to be continued for next year's annual conference. A call for proposals for HOPA sessions will be announced in early summer 2012. Guidelines detailing the application process for session proposal submission will be posted on the HOPA website soon. Now is the time to begin formulating ideas for session proposals!

Finally, it is not too early to begin planning your attendance for next year's conference. Mark your calendars now for the 2013 HOPA 9th Annual Conference! Next year's conference will be held March 20–23 in Los Angeles, CA.

Publications Committee

Lisa Savage, Chair
Brandy Strickland, Vice Chair

Thank you to all of the volunteers who expressed interest in writing for the HOPA newsletter this year as well as those who contributed articles. A special thank you to the Publications Committee members for your time, dedication, and expertise; *HOPA News* would not have been such an amazing success without you!

Standards Committee

LeAnne Kennedy, Chair
Barry Goldspiel, Vice Chair

The HOPA Standards Committee continues its work with the development of our first clinical practice guideline, *Investigational Medication Best Practice*. A draft outline has been finalized and authors have been selected. In the upcoming weeks, author assignments will be made.

Axitinib (Inlyta®)

Class: Vascular endothelial growth factor receptor (VEGFR) inhibitor

Indication: Treatment of advanced renal cell carcinoma after failure of one prior systemic therapy

Dose: 5 mg PO twice daily

Dose modifications
Coadministration with strong CYP3A4/5 inhibitors: increase axitinib dose by about 50%
Moderate hepatic impairment Child-Pugh class B: reduce axitinib dose by about 50%

Common adverse effects: Diarrhea, hypertension, fatigue, anorexia, nausea, dysphonia, palmar-plantar erythrodysesthesia syndrome, weight loss, vomiting, weakness, constipation, hypothyroidism

Serious adverse effects: Hypertensive crisis, arterial and venous thromboembolic events, hemorrhage, gastrointestinal perforation, fistula formation, reversible posterior leukoencephalopathy syndrome

Drug interactions: Strong inducers and inhibitors of CYP3A4/5; solubility is pH dependent, though no dose adjustment is required with antacids.

Axitinib for Renal Cell Cancer

Lisa Lohr, PharmD BCOP BCPS
Oncology Clinical Pharmacist/MTM Provider
Masonic Cancer Center (University of Minnesota/Fairview), Minneapolis, MN

Medications that inhibit the action of the vascular endothelial growth factor (VEGF) signaling pathway form the backbone of available therapy for renal cell cancer (RCC).[1] In RCC, VEGF can be overexpressed because of the loss of the Von Hippel-Lindau tumor suppressor gene. VEGF signaling leads to increased angiogenesis and tumor cell survival. Axitinib (Inlyta®) is a VEGF tyrosine kinase inhibitor that was approved January 27, 2012, for the treatment of RCC. Axitinib is a potent inhibitor of the three VEGF subtypes (VEGF-1, VEGF-2, and VEGF-3) and has additional activity against platelet-derived growth factor alpha (PDGFRβ) and the proto-oncogene c-KIT.

Axitinib was approved by the U.S. Food and Drug Administration (FDA) on the basis of a randomized, unblinded, phase 3 study (The AXIS trial) comparing axitinib to sorafenib in patients with RCC whose cancer had progressed after treatment.[6] Previous systemic treatment could have included sunitinib-, temsirolimus-, bevacizumab/interferon-alfa-, or cytokine-based treatment. Patients were excluded if they had a performance status of ≥2, poor life expectancy, poor renal and hepatic function, a need for CYP3A4 inhibitors or inducers, central nervous system metastases, or uncontrolled hypertension. Seven hundred twenty-three patients were randomly assigned to either treatment with axitinib 5 mg twice daily or sorafenib 400 mg twice daily. Dose increases for axitinib to 7 mg by mouth (PO) twice daily, then 10 mg PO twice daily were permitted in patients without hypertension or grade 2 or higher adverse event. Both agents were continued until tumor progression or the presence of unacceptable toxicity. Crossover from one treatment to the other was prohibited. The primary endpoint was progression-free survival (PFS); secondary endpoints included overall survival (OS), objective response (OR), duration of response, and time to deterioration. The dose of axitinib was increased to more than 5 mg PO twice daily in 37% of patients. Patients were treated with axitinib for a median of 6.4 months and sorafenib for 5.0 months. The median PFS was 6.7 (confidence interval [CI] 6.3–8.0) months in those treated with axitinib and 4.7 (CI 4.6–5.6) months in those treated with sorafenib, which was statistically significant. The impact of axitinib on PFS was even higher in patients previously treated with a cytokine-based regimen and lower in those previously treated with sunitinib. The OR rate (all partial responses) was 19% in the axitinib group and 9% in the sorafenib group. The median time to deterioration was longer in the axitinib group at 3.1 months (or 3.7 months, depending on the scale used) versus 2.8 (or 2.9) months in the sorafenib group. The authors of this study concluded that treatment with axitinib provided a significantly longer PFS than sorafenib in the second-line treatment of RCC. The authors noted that these results are consistent with the idea that axitinib can have a more profound clinical effect because it has a more potent VEGF inhibition.

The most common adverse effects seen in the trial with axitinib were diarrhea (55%), hypertension (40%), fatigue (39%), anorexia (34%), nausea (32%), dysphonia (31%), and palmar-plantar erythrodysesthesia (27%). The most common grade 3 or 4 toxicities seen with axitinib were hypertension (16%), diarrhea (11%), and fatigue (11%). In addition, the increased serum creatinine (55%), hypocalcemia (39%), anemia (35%), lymphopenia (33%), and lipase elevation (27%) were the most noted laboratory abnormalities; these were only rarely grade 3–4.

Hypertension was the dose-limiting toxicity found in phase 1 trials and may serve as a predictor of response. As with other oral VEGF inhibitors, patients with hypertension may have a more favorable response to axitinib compared with patients who do not have hypertension. From data pooled from phase 2 trials with axitinib, patients who had at least one diastolic blood pressure (DBP) ≥ 90 mmHg had an overall survival of 130 weeks, compared with 42 weeks seen in those who did not have a DBP ≥ 90 mmHg.[3]

The pharmacokinetics of axitinib have been well described.[2-5] Axitinib is moderately well absorbed, with a bioavailability of approximately 58%. Although axitinib can be taken with or without food, administration in the fasting state can increase the area under the concentration time curve (AUC) and maximum concentration observed (Cmax) of this medication. The tmax is at 2–6 hours after administration. The

half-life in the fasting state is about 4.8–5 hours, but it is about 2–2.3 hours when taken with food. Axitinib is predominantly metabolized by the liver, with only <1% excreted unchanged in the urine. It is metabolized primarily by CYP3A4, with some contribution by CYP1A2, CYP2C19, and UGT1A1. Ketoconazole, a strong inhibitor of CYP3A4, was shown to significantly increase the Cmax and the AUC of axitinib, while coadministration of the strong CYP3A4 inducer rifampin substantially decreases the Cmax and AUC. Axitinib may inhibit CYP1A2 and CYP2C8 but did not show alteration in the blood levels of paclitaxel, a CYP2C8 substrate.

For most patients, the starting dose of axitinib is 5 mg PO twice daily.[2] Doses can be taken with or without food but should be taken with a glass of water. If axitinib must be given with a concomitant strong CYP3A4/5 inhibitor, the dose should be reduced by approximately 50%. There is no need to adjust the initial dose in patients with mild hepatic impairment (Child-Pugh class A); however, in patients with moderate hepatic impairment (Child-Pugh class B), the axitinib dose should be reduced by approximately 50%. Axitinib has not been studied in patients with severe liver insufficiency. The dose of axitinib may be increased to 7 mg PO twice daily, and then to 10 mg PO twice daily in patients who are stable for at least 2 weeks, are not experiencing a grade 3 or 4 toxicity, and have normal blood pressure while not on antihypertensive medications. If dose reduction is needed due to adverse effects, axitinib should be reduced to 3 mg PO twice daily, and then to 2 mg PO twice daily, if required. Axitinib is marketed in 5-mg and 1-mg tablets.

Other serious but less common adverse effects include hypertensive crisis, arterial and venous thromboembolism, bleeding complications, gastrointestinal perforation, fistula formation, hypothyroidism, proteinuria, reversible posterior leukoencephalopathy syndrome, and increased liver function enzymes.

For patients starting on axitinib therapy, baseline assessment should include blood pressure, comprehensive metabolic panel, and urine for protein. Recommended monitoring of the patient should include frequent blood pressures (weekly at the beginning of therapy) as well as a comprehensive metabolic panel and urine protein monthly.

Axitinib has been studied in published phase 2 and phase 3 trials in cancers other than RCC. One group studied axitinib in a phase 3 trial in patients with advanced non-small-cell lung cancer and found that axitinib has activity in this group.[7] The rate of disease control (partial responses and stable disease) was 41%. Kindler and colleagues compared axitinib plus gemcitabine versus gemcitabine alone in patients with advanced pancreatic cancer.[8] Based on an interim analysis, it was found that there was no significant increase in PFS or OS. A third group studied axitinib plus docetaxel versus docetaxel alone in patients with metastatic breast cancer.[9] This phase 2 trial demonstrated no significant improvement in time to progression in the group treated with axitinib plus docetaxel; however, there was an improvement in time to progression in the combination arm in those patients who had received prior adjuvant chemotherapy. There are many other trials underway in patients with RCC as well as patients with many other cancers.

In conclusion, the VEGF inhibitor axitinib is effective in the second-line treatment of RCC. It is fairly well tolerated, with diarrhea, hypertension, and fatigue commonly reported in patients treated with axitinib. The dose should be adjusted in those with moderate hepatic impairment and those treated with concomitant CYP3A4/5 inhibitors. Additional studies are needed to further delineate the action of axitinib compared with other treatments for RCC.

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Glucarpidase (Voraxaze™)

Class: Antidote agent

Indication: Treatment of toxic plasma levels of methotrexate (>1 micromol/L) in adult and pediatric patients with delayed methotrexate clearance due to impaired renal function

Dose: Single injection of 50 units/kg, intravenous (IV) bolus over 5 minutes

Dose modifications: None

Common adverse effects/limitations of use: Glucarpidase should not be used in patients with normal or mildly impaired renal function due to the risk of subtherapeutic exposure to methotrexate. Adverse effects are uncommon (<2%) but include flushing, paresthesias, and nausea/vomiting.

Drug interactions: Leucovorin rescue should continue in conjunction with glucarpidase; however, leucovorin should not be administered within 2 hours before or after glucarpidase.

FDA Approves Glucarpidase for Treatment of Methotrexate-Induced Nephrotoxicity

Carrie Barnhart, PharmD
Clinical Pharmacist
Billings Clinic, Billings, MT

Severe treatment-related toxicity from high-dose methotrexate (MTX) is uncommon when leucovorin rescue and supportive care are implemented appropriately. However, MTX-induced nephrotoxicity still occurs in 2%–10% of patients and could result in treatment delays or potentially life-threatening adverse effects.[1] Precipitation of MTX in renal tubules is thought to be the primary mechanism for MTX-related renal failure, although direct tubular injury can also occur.[2] Renal failure causes decreased clearance of MTX, leading to prolonged exposure to toxic MTX blood levels.[1] Standard prophylactic measures to minimize MTX-induced nephrotoxicity include urine alkalinization (because MTX is poorly soluble in acidic urine) and aggressive intravenous hydration because volume depletion decreases urine flow rate and increases MTX concentration in tubular fluid.[2]

Glucarpidase is a carboxypeptidase enzyme that hydrolyzes the carboxyl-terminal glutamate residue from folic acid and antifolates such as methotrexate. Glucarpidase converts MTX to its inactive metabolites, 4-deoxy-4-amino-N10-methylpteroic acid (DAMPA) and glutamate, and provides a nonrenal route for methotrexate elimination.[3] Glucarpidase does not reduce intracellular concentrations of methotrexate, thus continuation of leucovorin is still required.[4] Glucarpidase has been available in the United States since 2007 through a compassionate-use, open-label trial program; it was approved by the U.S. Food and Drug Administration (FDA) in January 2012 for the treatment of toxic plasma MTX levels (>1 micromol/L) in patients with delayed methotrexate clearance due to impaired renal function.[3,4]

Two unpublished open-label, single-arm studies evaluated safety data in 290 adult and pediatric patients. A subset of these patients had efficacy measurements, and all 22 evaluated had >95% reductions in MTX concentrations.[4] In a separate evaluation of 100 patients receiving glucarpidase for MTX toxicity, delayed administration of glucarpidase >96 hours after initiation of MTX led to a higher risk of developing severe toxicity.[4] A retrospective review of 20 pediatric patients who received glucarpidase for acute renal injury due to high-dose MTX demonstrated a complete recovery of renal function in all patients (median 21 days).[5] Randomized controlled studies of glucarpidase in clinical outcomes, such as reducing MTX toxicity or improving survival, are lacking.

Methotrexate concentrations within 48 hours following administration of glucarpidase can only be reliably measured by a chromatographic method. One of MTX's inactive metabolites, DAMPA, interferes with the immunoassay measurement of MTX concentration, which can result in an overestimation of the value. Due to the long half-life of DAMPA ($t1/2$ of approximately 9 hours), measurement of MTX using immunoassays is unreliable for samples collected within 48 hours following glucarpidase.[3]

In the population of patients receiving high-dose methotrexate and glucarpidase, it may be difficult to discern which drug may be causing adverse effects, though glucarpidase is generally well tolerated. In clinical trials, the most common adverse effects occurred in <2% of patients and included paresthesias, flushing, nausea and vomiting, headache, and hypotension. There was one grade-3 event of flushing; all other adverse effects were grade 1–2.[3]

Leucovorin administration should continue after high-dose MTX. Do not administer leucovorin 2 hours before or 2 hours after glucarpidase because leucovorin is a substrate of glucarpidase.[3] Administration of glucarpidase within 2 hours of leucovorin reduced the area under the curve (AUC) of leucovorin and its active metabolite by 33% and 92%, respectively.[4]

Glucarpidase is administered as a single IV bolus of 50 units/kg over 5 minutes. It is supplied lyophilized in vials of 1,000 units. Reconstituted glucarpidase should be used immediately but can be stored under refrigeration for up to 4 hours.[3]

Glucarpidase is an important antidote that rapidly reduces toxic methotrexate levels in patients with renal impairment. Its administration needs to be separated by at least 2 hours from leucovorin. The effect of glucarpidase on reducing clinical effects of methotrexate toxicity or improving survival requires further study.

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Nominations for HOPA Membership Awards Now Being Accepted

Hematology/Oncology Pharmacy Association

hoparx.org

The HOPA Nominations & Awards Committee is now accepting nominations for the 2013 Membership Awards Program. Learn more and nominate a qualified candidate today at www.hoparx.org. The deadline for nominations is October 1, 2012.

Vismodegib (Erivedge™)

Class: Hedgehog pathway inhibitor

Indication: Treatment of metastatic basal cell carcinoma or locally advanced basal cell carcinoma that has recurred following surgery or in patients who are not candidates for surgery or radiation therapy

Dose: 150 mg orally once daily until disease progression or unacceptable toxicity

Dosage form: Oral capsule

Common adverse effects: Muscle spasms, alopecia, dysgeusia, fatigue, anorexia, nausea, diarrhea, constipation, weight loss, arthralgias

Serious adverse effects: Diarrhea, nausea, hyponatremia, weight loss

Drug interactions
P-glycoprotein substrate: Coadministration with P-gp inhibitors (e.g., clarithromycin, erythromycin, azithromycin) can cause an increase in exposure to vismodegib.
Drugs that can increase pH of the stomach can decrease bioavailability of vismodegib. Separate vismodegib from antacids or H2 blockers by several hours. Avoid concurrent use of vismodegib with a proton pump inhibitor (PPI). If a PPI is necessary, monitor for decreased efficacy of vismodegib. Increasing the dose of vismodegib will not overcome the decrease in bioavailability.

Monitoring: Pregnancy test within 1 week prior to treatment initiation

Pregnancy and nursing: Due to the embryotoxic, fetotoxic, and teratogenic effects observed in animal reproduction studies, patients of child-bearing age should verify pregnancy status prior to initiating therapy with vismodegib. Men taking vismodegib should use barrier protection during intercourse because of the potential risk of exposure to the drug through semen. Women should use an effective method of contraception to avoid pregnancy while taking this drug. Women should not nurse while taking this medication.

Warnings: Patients should be advised not to donate blood while on this medication or for a minimum of 7 months after discontinuing.

First Hedgehog Pathway Inhibitor Approved for Basal Cell Carcinoma

Renee Curtis, PharmD
Clinical Oncology Pharmacist
The Everett Clinic, Everett, WA

Basal cell carcinoma (BCC) is a common cancer of the skin that can be aggressive and cause destruction of the skin and surrounding tissue. The treatment approach is dependent on how advanced the tumor is and the risk for recurrence. BCCs at low risk for recurrence are generally treated with electrodessication and curettage or surgical excision. Superficial lesions in noncritical areas can be treated with topical 5-fluorouracil cream or with photodynamic therapy. There is no standard therapy in locally advanced or metastatic basal cell cancers.

Metastatic rates for BCC are very low. The most common sites for metastasis to occur are lymph nodes, lung, bones, skin, and liver. The prognosis for metastatic basal cell carcinoma (mBCC) is poor, with a mean survival of 8 months.[1]

Vismodegib represents the first in a new class of agents that target the Hedgehog (Hh) signaling pathway and is indicated for the treatment of adults with mBCC or locally advanced basal cell carcinoma (laBCC) that has recurred following surgery or who are not candidates for surgery or radiation therapy.[2] In the Hh pathway, the homologue Patched 1 (PTCH1) inhibits Smoothened (SMO), which is an activator in the pathway. When the PTCH1 ligand is bound by signaling proteins, it loses the ability to suppress SMO, which in turn signals the activation of gene transcription to allow cell proliferation. Vismodegib targets SMO to turn off the Hh pathway.[3]

VonHoff and colleagues conducted an open-label, multicenter, two-stage phase 1 trial involving 33 patients with mBCC or laBCC who received vismodegib at a dose of 150 mg daily (*n* = 17), 270 mg daily (*n* = 15), or 540 mg daily (*n* = 1). Stage 1 was the dose ranging stage, while stage 2 examined pharmacokinetics. Eighteen of the 33 patients had an objective response; two patients experienced a complete response (CR), and 16 had a partial response (PR). Eleven of the 33 patients had stable disease and four had progressive disease. The median length of treatment was 9.8 months, and the median duration of response was 8.8 months.[4] Another phase 1 trial enrolled 68 patients who received 150 mg (*n* = 41), 270 mg (*n* = 23), or 540 mg (*n* = 4) for a variety of tumor types including BCC (*n* = 3), pancreatic cancer (*n*= 8), medulloblastoma (*n* = 1), and other tumor types (*n* = 17). This study showed encouraging results, warranting further research.[5]

A single-arm, multicenter, open-label cohort trial looking at patients with mBCC or laBCC was conducted. The study enrolled 104 patients, 33 of whom were diagnosed with mBCC and 71 with laBCC. Patients were treated with 150 mg of vismodegib daily. The efficacy outcome measure of the trial was objective response rate (ORR). Ninety-six patients were evaluable for ORR. The median duration of treatment was 10.2 months (range, 0.7–18.7 months). In the mBCC group, 30.3% of patients had an ORR and all were PR (no patient achieved a CR). In the laBCC group, 42.9% (*n* = 27) of patients had

an ORR; of those patients, 51.8% (*n* = 14) and 48.1% (*n* = 13) achieved a PR and CR, respectively. The median response duration in both groups was 7.6 months.[2]

The most common adverse reactions seen in studies (all grades) included muscle spasms (71.7%), alopecia (63.8%), dysgeusia (55.1%), weight loss (44.9%), fatigue (39.9%), nausea (30.4%), diarrhea (29%), anorexia (25.4%), constipation (21%), and arthralgias (15.9%). Grade 3–4 toxicities have included weight loss (grade 3, 7.2%), fatigue (grade 3, 5.1%; grade 4, 0.7%), muscle spasms (grade 3, 3.6%), and anorexia (grade 3, 2.2%). Fewer than 1% of patients experienced grade 3 toxicities with regard to nausea, diarrhea, and arthralgias. Hyponatremia (4%), azotemia (2%), and hypokalemia (1%) were the grade 3 laboratory abnormalities experienced by patients in clinical trials.[2] Vismodegib does carry a black box warning regarding embryo-fetal death and severe birth defects. Due to its embryotoxic, fetotoxic, and teratogenic effects observed in animal reproduction studies, patients of child-bearing age should verify pregnancy status prior to initiating therapy with vismodegib. Men taking vismodegib should use barrier protection during intercourse because of the potential risk of exposure to the drug through semen. Women should use an effective method of contraception to avoid pregnancy while taking this drug, and women should not nurse while taking this medication.

Vismodegib elimination occurs via multiple pathways and is primarily excreted as unchanged drug. In vitro studies show that vismodegib is a CPY2C9 and 3A4 substrate, though patients in clinical trials who were treated with concomitant CYP 3A4 inducers and inhibitors demonstrated similar plasma vismodegib levels to those who did not receive these medications. Vismodegib is a p-glycoprotein (p-gp) substrate; thus, coadministration with P-gp inhibitors (e.g., clarithromycin, erythromycin, azithromycin) can cause an increase in exposure and risk of adverse effects. Drugs that can increase the pH of the stomach can decrease bioavailability of vismodegib. Separate vismodegib from antacids or H2 blockers by several hours. Avoid concurrent use of vismodegib with a proton pump inhibitor (PPI). If a PPI is necessary, monitor for decreased efficacy of vismodegib. Increasing the dose of vismodegib will not overcome the decrease in bioavailability.

The starting dose for vismodegib is 150 mg orally once daily (until disease progression or unacceptable toxicity occurs) and is supplied as a 150-mg oral capsule. It can be taken without regard to food and should be swallowed whole; do not open the capsule or crush it.

The Hh pathway has been an exciting target since pathway hyperactivity has been implicated in the development of medulloblastomas and BCCs. However, this excitement may come with a downside. In a case study of a metastatic medulloblastoma patient who had a very dramatic response to vismodegib therapy, it was discovered that resistance may have rapidly developed through mutations in the PTCH and SMO sequencing. It is suggested that second generation Hh inhibitors may need to be developed to overcome this acquired resistance.[6,7]

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Wrapping Up the HOPA 8th Annual Conference

More than 700 hematology/oncology pharmacists attended this year's annual conference at the Hilton Orlando in Florida. The Oncology Boot Camp kicked off the conference with nearly 200 new practitioners and pharmacists and was a resounding success. Highlights from the Boot Camp included sessions on cell cycle control, angiogenesis, and mitogenic signaling and need-to-know information about tyrosine kinase inhibitors.

The conference boasted an array of impressive educational sessions, poster presentations, BCOP review sessions, and networking opportunities for new and experienced pharmacists. New this year was the Clinical Pearls session, which introduced four clinical improvements to integrate into practice including managing hypersensitivity reactions, use of enoxaparin and methylene blue as a treatment for ifosfamide-induced encephalopathy, and safe use of arsenic trioxide in acute promyelocytic leukemia. Another innovation for this year's conference was a practice issues panel on drug shortages. Panelists from pharmacy practice, academia, and the U.S. Food and Drug Administration presented their perspectives on the growing drug shortage problems.

As a result of what you learned at conference, how will your practice change?

"Form a formulary team, make a policy for drug cost evaluations, and conduct research on outcomes in adolescents and young adults (AYAs) in our institution."

"Venous thromboembolism treatment in obese patients, knowledge of correct therapeutic regimens in different cancer types enhanced."

In other general sessions, updates on infectious diseases were presented and research platform presentations featured top research abstracts from 2012.

The exhibit hall hosted 40 booths, providing attendees access to state-of-the-art products, services, and information pertinent to the demands of oncology pharmacy. In addition, the conference featured a corporate showcase presented by Novartis Pharmaceutical and a Career Fair with 8 participating facilities.

Susan Goodin, PharmD, was awarded the 2012 HOPA Award of Excellence for her contributions to the field of hematology/oncology pharmacy. Other award recipients included Dan Zlott, PharmD MS BCOP, for the New Practitioner Award; Cindy O'Bryant, PharmD BCOP FCCP, for the Basic Science and Clinical Research Literature Award; and Kristine Crews, PharmD BCPS, for the Oncology Practice Literature Award.

Early Saturday morning, new and experienced yoga practitioners came out to welcome the day and participate in a yoga session. The Rays of Hope event raised money for the Give Hope Foundation.

It was wonderful to see so many members connecting with colleagues and forging new relationships during this year's conference. We look forward to seeing you next year at HOPA's 9th Annual Conference in Los Angeles, CA, March 20–23, 2013.

"Recommend more involvement in patient assistance programs; recommend more options with myelofibrosis; recommend collaboration with our children's hospital when caring for AYA patients."

Based on information provided at the 2012 HOPA Annual Conference, attendees share how they will change their practice.

"I am planning to start an oral chemo counseling program in our community cancer center. I will also incorporate many other miscellaneous 'pearls' that I picked up throughout the conference, including networking with colleagues."

"The information presented . . . will enhance my ability to discuss and explain new therapies to patients and provide me with a better understanding and expanded knowledge base."

"I would like to work on a better plan for hypersensitivity reactions, take a closer look at the biosimilar data, and work on oral medication patient education in our institution."

"I currently practice mostly inpatient, but will try to shift my focus to the outpatient setting to better utilize the knowledge gained from attending HOPA meetings."