Hematology/Oncology Pharmacy Association

HOPA News

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A New Indication for Everolimus: Advanced Hormone Receptor-Positive Breast Cancer in Postmenopausal Women in Combination with Exemestane

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Hormone receptor-positive (HR+) breast cancer is the most commonly diagnosed form of breast cancer.[1] Endocrine therapy is the standard of care for patients with HR+ breast cancer and includes selective estrogen receptor (ER) modulators (e.g., tamoxifen) and aromatase inhibitors (e.g., letrozole, anastrazole, exemestane). Despite significant clinical benefits with these drugs, de novo and acquired endocrine resistance are major clinical challenges in the treatment of HR+ breast cancer.[1] One of the mechanisms of endocrine resistance is aberrant phosphatidylinosine 3-kinase (PI3K)/AKT signaling, which is mediated by mammalian target of rampamycin (mTOR).[1,2] In preclinical models of endocrine resistance, pharmacological inhibition of the PI3K/AKT/mTOR pathway has been shown to overcome drug resistance.[2] Everolimus is an inhibitor of the mTOR pathway and has been approved by the U.S. Food and Drug Administration (FDA) under the brand name Afinitor® for the treatment of adults with progressive neuroendocrine tumors of pancreatic origin, advanced renal cell carcinoma, renal angiomyolipoma, and tuberous sclerosis complex (TSC), and for pediatric and adult patients with TSC who have subependymal giant cell astrocytoma.[3] Everolimus also has been marketed under the brand name Zortress® and is approved for the treatment of adult patients with renal transplant.[4]

In July 2012 the FDA granted approval of everolimus in combination with exemestane for the treatment of postmenopausal women with advanced HR+, human epidermal growth factor receptor-2-negative (HER2-) breast cancer resistant to nonsteroidal aromatase inhibitors (letrozole or anastrazole).[3] The approval was based on the results of a randomized, double-blind, placebo-controlled multicenter phase 3 BOLERO-2 trial conducted in 724 postmenopausal women with HR+, HER2- advanced breast cancer experiencing recurrence or disease progression after previous therapy with letrozole and anastrazole.[5] Patients were randomized 2:1 in either the everolimus 10 mg/day plus exemestane 25 mg/day arm or placebo plus exemestane 25 mg/day arm. The baseline characteristics

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Send administrative correspondence or letters to the editor to HOPA, 4700 W. Lake Avenue, Glenview, IL 60025, 877.467.2791, fax 847.375.6497, e-mail info@hoparx.org. *HOPA News* is published by the Hematology/Oncology Pharmacy Association.

were well balanced between the two groups, with a median age of 62 years. Visceral organ involvement was seen in 56% of patients, 76% of patients had bone metastasis, and 36% of patients had metastasis in at least three organs. According to local assessment, 72% of patients had progesterone receptor-positive tumors. A median of three prior therapies was received by patients and included letrozole or anastrazole (100%), tamoxifen (48%), fulvestrant (16%), and chemotherapy (68%). Previous sensitivity of endocrine therapy was documented in 84% of patients. The median treatment duration for exemestane plus everolimus was 14.6 weeks compared with 12 weeks of exposure to exemestane plus placebo. The primary reason for discontinuation of therapy was disease progression (37% in exemestane plus everolimus versus 66% in exemestane plus placebo). Patients in the placebo group were not permitted to cross over to everolimus at the time of disease progression. The primary end point was progression-free survival (PFS). Secondary endpoints included overall survival (OS), response rate (RR), and safety. According to assessment by local investigators, the PFS was more than double in the everolimus plus exemestane group (7.8 months) compared with the placebo plus exemestane group (3.2 months; hazard ratio [HR] 0.45; 95% confidence interval [CI] 0.38–0.54; $p < .0001$).[3] These PFS results were confirmed when assessed by an independent central radiological group and were consistent across the subgroups of age, race, presence and extent of visceral metastases, and sensitivity to prior hormonal therapy. The objective RR based on local assessments was 12.6% in the combination therapy arm and 1.7% in the placebo plus exemestane group ($p < .001$).[3] An interim analysis of OS did not show a statistically significant difference between the two treatment arms (HR 0.77; 95% CI 0.57–1.04).[3] The final analysis of OS data is expected to be completed in June 2014.

Everolimus was generally well tolerated.[3,5] The most common adverse reactions (≥30% incidence in everolimus plus exemestane versus placebo plus exemestane group) were stomatitis (67% versus 11%), infections (50% versus 25%), rash (39 % versus 6 %), fatigue (36% versus 27%), diarrhea (33% versus 18%), and decreased appetite (30% versus 12%). Overall, the most common grade 3 or 4 adverse reactions (≥2% incidence) were stomatitis (8% versus 1%), infections (5% versus 2%), hyperglycemia (4 % versus <1 %), fatigue (4% versus 1%), dyspnea (4% versus 1%), pneumonitis (4% versus 0%), and diarrhea (2% versus 1%). The addition of everolimus to exemestane was associated with more fatal adverse reactions (2% versus <1%), more treatment discontinuation due to adverse reactions (24% versus 5%), and more dose interruptions or reductions (63% versus 14%).[3,5] The everolimus plus exemestane arm included 40% of patients ≥25 years of age and 15% of patients ≥75 years of age. Treatment discontinuation due to adverse reactions was more common in patients ≥65 years old compared with patients <65 years of age (33% versus 17%).[3]

In addition to the BOLERO-2 trial, other studies have shown clinical efficacy of everolimus in combination with different endocrine therapies in postmenopausal women with HR+ breast cancer in both the metastatic (TAMRAD study) and neoadjuvant settings.[6,7] In the phase 2 TAMRAD study, everolimus combined with tamoxifen significantly increased clinical benefit rate (61% versus 42%), time to progression (8.6 months versus 4.5 months), and OS (HR 0.45; 95% CI 0.24–0.81; $p < .007$) compared with tamoxifen alone in postmenopausal women with HR+, HER2-, metastatic breast cancer resistant to aromatase inhibitors.[6] In the neoadjuvant setting, the addition of everolimus to letrozole therapy for 4 months significantly improved the RR in treatment-naïve postmenopausal women with operable ER+ breast cancer (68.1% versus 59.1%).[7] In a biomarker subanalysis of this neoadjuvant study, more patients in the everolimus plus letrozole group had Ki67 reduction (a measure of antiproliferative effect) in tumor tissues collected after 2 weeks of treatment compared with the placebo plus letrozole group.[7] Furthermore, patients with activating PIK3CA mutations in the exon 9 helical domain, which is associated with poor outcomes, showed better antiproliferative response when everolimus was added to letrozole.[7] The safety profile of everolimus in both these studies was consistent with what is reported in the BOLERO-2 trial. These phase 2 studies indicate that everolimus may have clinical utility in combination with various endocrine therapies in different treatment settings.

The 10-mg daily dosing regimen of everolimus is based on a pharmacokinetic (PK)-pharmacodynamic (PD) modeling[8] of preclinical and clinical data showing dose- and schedule-dependent inhibition of the mTOR pathway with everolimus.[9] This was supported by a clinical study

comparing 10-mg daily and 70-mg weekly schedules of everolimus in patients with advanced breast cancer.[10] Therefore, additional dose-optimization studies are not warranted, at least at this point.

Everolimus represents a new therapeutic option for the treatment of postmenopausal women with HR+, HER2- advanced breast cancer resistant to nonsteroidal aromatase inhibitors. Based on the promising clinical findings of the BOLERO-2 and TAMRAD studies, everolimus is now included in the National Comprehensive Cancer Network guidelines.[11] However, the benefit of everolimus for improving long-term outcomes (i.e., OS) in the BOLERO-2 study still remains to be seen. Additional correlative biomarker studies are essential for identifying the patient population that can most benefit from everolimus therapy and whether there is a relationship between the presence of PIK3CA mutations and its efficacy.

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Alemtuzumab (Campath): New Indications and Distribution Program

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Alemtuzumab was withdrawn from the U.S. commercial market on September 4, 2012. The drug remains available (free of charge) for select indications through the U.S. Campath Distribution Program. The withdrawal is an attempt to prevent off-label alemtuzumab use as the manufacturer plans to reintroduce alemtuzumab under a different brand name with a multiple sclerosis indication. To receive alemtuzumab, healthcare providers must now comply with certain requirements. There are two separate processes for acquiring and dispensing the drug. The first process is reserved for patients receiving a solid organ transplant who require induction therapy with alemtuzumab. The second is to be utilized for patients with all other indications.

Solid Organ Transplant Process

The Campath Distribution Program will provide us with a ready inventory of alemtuzumab for induction therapy in patients receiving solid organ transplants. The stock supply is not patient specific. Although solid organ transplant recipients do not require enrollment in the program prior to administration of the drug, pharmacies must document patient information at the time of dispensing for stock replenishment purposes. A transplant institution replenishment form must be completed and include the following:

- diagnosis code
- procedure code
- date of administration
- lot number
- number of vials used
- the provider's signature.

Patient-Specific Request Process

The patient-specific request process is necessary to acquire alemtuzumab for indications other than solid organ transplant induction therapy. It requires patient enrollment in the distribution program and acquisition of patient-specific stock. Other indications for alemtuzumab may include chronic lymphocytic leukemia, acute lymphocytic leukemia, and steroid-resistant kidney transplant acute rejection.

For additional information on the U.S. Campath Distribution Program, visit www.campath.com.

Important Contact Numbers

Campath Distribution Program: 1.877.422.6728
Genzyme Medical Information: 1.800.745.4447 Option 2

FDA Approves the Therascreen® KRAS RGQ PCR Kit

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Cetuximab is a chimeric monoclonal antibody that competitively inhibits the binding of ligands to the epidermal growth factor receptor (EGFR), resulting in inhibition of cell growth and induction of apoptosis.[1] Mutations in the KRAS protein, found downstream of the EGFR protein, can cause KRAS to remain active despite EGFR inhibition. Studies have demonstrated that patients with mutations of the KRAS gene do not benefit from treatment with cetuximab.[1,2] The U.S. Food and Drug Administration (FDA) updated the approval criteria for cetuximab for metastatic colorectal cancer treatment, indicating that the drug should only be used in patients with EGFR-expressing KRAS wild-type tumors as determined by FDA-approved tests.[1] This necessitated the development of an FDA-validated diagnostic test to determine KRAS mutation status. In July 2012 the FDA approved the therascreen® KRAS RGQ PCR Kit (Qiagen Manchester, LTD), a genetic test designed to determine the presence of mutations in the KRAS gene in colorectal cancer cells.[3]

The therascreen KRAS RGQ PCR kit uses allele-specific polymerase chain reaction (PCR) on DNA samples of colorectal cancer tissue that have been embedded in paraffin. The test is designed to provide a quantitative assessment of the seven most frequent mutations in codons 12 and 13 of the KRAS oncogene.[4] The lower limit of detection for the mutations ranges from 0.8%–6.4% compared with conventional bidirectional DNA sequencing, which has a lower limit detection of 15%–25%.[5] Validation for the test was conducted using tissue samples obtained from patients with metastatic colorectal cancer who enrolled in a phase 3 clinical trial of cetuximab plus best supportive care versus best supportive care alone.[2] Results demonstrated that overall survival was significantly longer in patients with KRAS wild-type tumors who received cetuximab. There was no survival benefit seen with cetuximab in patients with KRAS-mutated tumors, as detected by the therascreen KRAS RGQ PCR kit.[2,3] The therascreen KRAS RGQ PCR kit was able to detect the presence of KRAS mutations with 85% concordance with bidirectional DNA sequencing.[2]

In addition to approving the therascreen KRAS RGQ PCR kit, the FDA also approved cetuximab for use in combination with FOLFIRI for first-line treatment of metastatic colorectal cancer.[3] The package labeling states that cetuximab should only be used in patients with KRAS wild-type EGFR-expressing tumors, as determined by FDA-approved tests.[1] This requires that tumor tissue samples from patients be sent to laboratories that offer the therascreen KRAS test. A list of laboratories that currently offer this test is available on the Qiagen website.[6] The approval of the validated test that quantitatively identifies mutations on the KRAS gene may allow healthcare providers to more quickly and accurately identify patients who may benefit from cetuximab therapy (the typical turnaround time for results from a therascreen kit is a half day). If an institution is capable of running polymerase chain reactions in-house, this turnaround time could be further decreased.

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HOPA's First Hill Day

Lisa Holle, PharmD BCOP, HOPA President

One of the goals of the current HOPA strategic plan is to ensure that HOPA and its members are recognized as important partners by the pharmacy and cancer communities and are able to influence decisions affecting the care of cancer patients. One strategy used to achieve this goal is to educate legislators about HOPA and the value and role that hematology/oncology pharmacists play in healthcare delivery and health policy priorities. Although letters, e-mails, and phone calls are all methods that can be used to communicate with legislators, an in-person visit certainly is one of the most effective methods to have your message heard.

After attending the National Coalition for Cancer Research member meeting on September 13 in Washington, DC—along with Erin Morton of Drinker, Biddle & Reath, our government relations firm—I headed to Capitol Hill to begin the first formal introductions of HOPA. The goal was to meet with the senators and a representative from Connecticut (my state) because getting appointments is easier when you are a constituent of the legislator's district. I also planned to meet with other legislators who have been or are involved in introducing legislation related to HOPA's key health policy priorities: drug shortages and oral chemotherapy.

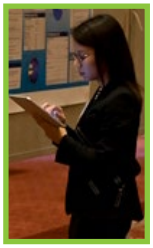
As luck would have it, we were able to make four appointments, which is not easy to do when legislators are in session. First, we met with Representative Joe Courtney (D-CT) and his staff. We provided him with an overview of HOPA and our healthcare policy agenda, leaving him with an information packet that contained completed issue briefs (1–2-page summaries outlining key health policy priorities), and discussed national oral chemotherapy parity legislation that Senator Al Franken (D-MN) is planning to introduce soon. Representative Courtney often supports healthcare-related legislation and, upon hearing that Connecticut already had a law in place, was enthusiastic about the proposed federal legislation.

Next we were able to meet with Senator Franken's healthcare legislative assistant. Because Senator Franken is planning on introducing oral chemotherapy parity legislation, his staff was interested to learn that one of HOPA's health policy agenda items is improved access to oral chemotherapy, that we are part of the Patients Equal Access Coalition, and that several HOPA members have advocated for state-level legislation concerning oral chemotherapy reimbursement parity. We also learned that Senator Franken is a supporter of pharmacists, which may be helpful for future HOPA initiatives.

Finally, we met with the staff from Senators Richard Blumenthal (D-CT) and Joseph Lieberman (I-CT). During each of these meetings we were able to introduce the senators to HOPA, our health policy agenda, and the upcoming proposed oral chemotherapy parity legislation. It was very rewarding to meet with all of the Hill staffers. It was satisfying to learn that Representative Courtney understands the importance of our role in the delivery of patient care and the work of HOPA. Talking to these officials was much easier than I had imagined, and I left each visit feeling as if we had successfully met HOPA's goal of reaching out to elected officials to convey our advocacy agenda. In fact, just this past week, I was at a function with Representative Courtney and he immediately recognized me, remembered our visit, and asked about the oral chemotherapy parity legislation status. I think this does confirm that our first HOPA Hill day was successful.

For more information about HOPA's health policy agenda and activities and to sign up for our policy and advocacy e-mail list, please visit the HOPA Health Policy and Advocacy Web page at www.hoparx.org/Health-Policy/default/health-policy-advo.html.

2013 HOPA Travel Grants to the HOPA Annual Conference



- Forty grants are awarded.
- Each grant is for $500.
- The application deadline is January 7, 2013.

Apply today!

The National Marrow Donor Program System Capacity Initiative: Changing the Pharmacy Practice Paradigm

Tippu Khan, PharmD BCOP
Clinical Pharmacist–BMT
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The National Marrow Donor Program (NMDP) projects dramatic growth in the number of allogeneic hematopoietic cell transplants (HCTs) in the next few years, increasing from 5,000 allogeneic HCTs in 2010 to 12,500 in 2015. This increase is primarily due to advancements in HCT technology and supportive care, the introduction of reduced-intensity conditioning regimens, expanded use of alternative graft sources, and the emerging indications for HCT.

Because demand for allogenic HCT is currently surpassing the infrastructure, the NMDP initiated a 3-year project called the System Capacity Initiative (SCI) to gather core members of the HCT team to help generate solutions to this looming problem. With the leadership of Helen Leather, the NMDP SCI Pharmacy Workgroup was formed to identify solutions to problems facing the HCT pharmacy workforce. The pharmacy workgroup recognized that the complex situation encompasses both short-term issues, such as pharmacy advocacy, appropriate utilization of pharmacist skills, work hours, and retention, and long-term issues, such as outreach, education, and recruitment.

Short-Term Issues (or Rather, Solutions)

It has become clear that the probability of increasing the number of pharmacist positions during this economic climate is very low. One possible solution to the shortage would be to create more opportunities for partnerships between different layers of the pharmacist team. To this end, the work group is focusing its energy on the following projects:

1. The American Society of Blood and Marrow Transplantation (ASBMT) Pharmacy Special Interest Group (SIG): Previously, pharmacists did not have representation in the national HCT organization, so the group has worked extremely hard to create a pharmacy SIG that will help raise the profile of HCT pharmacists as core members of the team and provide an outlet for those pharmacists working in HSCT to network and share ideas. Though challenges remain, this is the first step toward furthering the profession in the area of HCT.
2. Collaborative practice agreement (CPA) white paper: Under the leadership of Julie Merten, pharmacists collaborated to write a best practices paper for publication in the *Hematopoietic Stem Cell Transplantation* journal to provide a framework for implementing a CPA and address how it may improve HCT program capacity. Early efforts engaging in collaborative practice with credentialed pharmacists to manage therapeutic drug monitoring, chronic medical conditions, and supportive care in HSCT recipients may be cost-effective and enable physicians to spend more time on new or more complex patients.
3. Liaising with the Foundation for the Accreditation of Cellular Therapy (FACT): The Centers for Medicare & Medicaid Services, acknowledging that pharmacists play a pivotal role in solid organ transplantation, has made it easier to justify pharmacist positions. The workgroup is currently working with FACT to establish similar guidelines to recognize the fundamental role and need for pharmacists on the HCT service.
4. Tiered pharmacist model white paper: One proposed strategy to help ameliorate the shortage of clinical pharmacy specialists is the development of a tiered pharmacy practice model that allows for the delivery of pharmaceutical care with the available resources within an institution. In this patient-centered care model, delivery of pharmaceutical care is optimized by refining and redistributing pharmacist responsibilities to different team members based on their expertise (e.g., technicians, clinical pharmacists with a general background, clinical pharmacists with HCT training). Currently, an NMDP SCI pharmacy subgroup is collaborating to generate a white paper that provides recommendations to appropriately utilize pharmacists with varied levels of training and responsibility.

Eye to the Future (and Navigating Potential Pitfalls)

The workgroup initially conducted a survey to assess the problems that the pharmacy community felt we faced. The survey clearly highlighted that despite working long hours, most HCT pharmacists love their jobs. Although most people may consider the long hours a deterrent, the value of our role is rewarding and may encourage more practitioners to practice in the setting of transplantation.

Unfortunately, for our specialty to grow we have to train more pharmacists in the intricacies of HCT. We cannot wait for the residency pool to overcome the market shortage. To encourage interest in the specialty, the workgroup has created a 2-day live course, "Fundamentals of Hematopoietic Stem Cell Transplantation Training Course," which is designed to teach a new practitioner the fundamental skills required to care for complex HCT patients. This course will be open to all providers (MDs, advanced practice professionals, RNs, and PharmDs) and run concurrently with the ASBMT/Center for International Blood and Marrow Transplant Research Tandem Meeting in Salt Lake City, UT, February 13–14, 2013. Practitioners can register for the course at www.eiseverywhere.com/ereg/newreg.php?eventid=43345&.

Boosting interest in HCT with young practitioners and students is one of our long-term objectives. The workgroup, partnering with HOPA, is providing a live "HCT Boot Camp" session at the next HOPA annual conference. This boot camp will help provide a primer on the major issues in HCT, such as graft-versus-host disease and common infections. Oncology practitioners should also expect to learn how to manage several major emergent problems that arise in the HCT population.

The workgroup is developing a social media presence, attempting to reach students and learners outside of the traditional spectrum of pharmacist marketing. Our hope is that by attempting to promote the value of a career in HCT through different means and venues, we will be able to reach people who might consider a career in HCT.

Rome Wasn't Built in a Day (or by One Person)

These projects would not have seen the light of day without the vision of Jeffrey W. Chell MD, NMDP chief executive officer, and Edward

Snyder MD, NMDP Board of Directors. The unending capacity of Lyndsey Aspaas, Pam Robinett, and Susie Burke helped keep our high-maintenance demands in check during these past 2 years. The NMDP SCI Pharmacy Workgroup includes Helen Leather, BPharm BCOP (chair); Laura Wiggins, PharmD BCOP (vice-chair); Joe Bubalo, PharmD BCPS; Ashley Morris Engemann, PharmD BCOP; Chris Fausel, PharmD BCPS BCOP; Alison Gulbis, PharmD BCOP; Cindy Ippoliti, PharmD (2010–2011); Tippu Khan, PharmD BCOP; Scott Lanum, PharmD BCOP; Julie Merten, PharmD BCPS; Jamie Shapiro, PharmD BCOP; Sepideh Shayani, PharmD; Connie Sizemore, PharmD; Tracey Walsh-Chocolaad, PharmD BCOP; and Casey Williams, PharmD BCOP.

The initial grant for the NMDP SCI covered 3 years. We are now at the end of the formal NMDP SCI, but the important projects will be carried forward under the ASBMT Pharmacy SIG. Working on these initiatives has been a labor of love for many of us among the HCT pharmacist community. A lot of people volunteered many nights and weekends to get these projects off the ground. If you get a chance, commend them on all their hard work. They are helping to change the practice of HCT pharmacy.

Editorial

The National Marrow Donor Program System Capacity Initiative: Changing the Pharmacy Paradigm

Lisa M. Holle, PharmD BCOP, HOPA President

In September I was invited by the National Marrow Donor Program (NMDP) System Capacity Initiative (SCI) Pharmacy Workgroup to attend the "SCI Year III: From Inquiry to Implementation" workshop. The initial invitation to attend was based on the premise of learning about this initiative to better understand future requests for collaboration from the NMDP SCI Pharmacy Workgroup, and I definitely found the workshop to be a truly great experience. The work that the NMDP SCI Pharmacy Workgroup has done in 3 short years is fantastic and lays the foundation for having pharmacists be recognized and used as core team members in the hematopoietic cell transplantation (HCT) setting. During the meeting, it was clear that although many institutions view pharmacists as core team members in the care of patients undergoing HCT, this is not true for all institutions. In addition, other healthcare team members may not understand the education and training these pharmacists receive, the additional roles they can undertake, or the value they can provide in this setting. This lack of understanding about the role of hematology/oncology pharmacists is not unique. In fact, that is one of the main advocacy efforts of HOPA: to promote and improve patient safety by realizing the value and role that hematology/oncology pharmacists play in healthcare delivery. As I travel to meetings like this, I not only introduce and represent HOPA, but also continue to promote the value of pharmacists in the care of patients with cancer. I encourage you to do the same, just as the NMDP SCI Pharmacy Workgroup has.

Announcing the "Day in the Life of a HOPA Pharmacist" Photo and Caption Contest

Submissions will be accepted November 1, 2012–January 18, 2013.

Everyone is a winner! Receive 1 month free membership for each submission (up to three). Visit www.hoparx.org for details.

Board Update

Lisa M. Holle, PharmD BCOP, HOPA President

Unexpected Delay in HOPA's Efforts for BCOP Recertification Program Bid

Since HOPA's formation, our members have continually supported having the organization take a greater role in the coordination of Board Certified Oncology Pharmacist (BCOP) recertification. The Board of Pharmaceutical Specialties (BPS) requires an organization seeking the ability to provide a BCOP recertification pogram to have a sustained track record in funding, personnel, and success in educational programming. During HOPA's 2010 strategic planning it was decided that the association was ready to submit a plan to BPS. HOPA worked with its members to prepare a comprehensive proposal to submit to BPS this fall, and notified BPS, the American College of Clinical Pharmacy (ACCP), and the American Society of Health System Pharmacists (ASHP) of our intent. Unfortunately, we have recently learned that BPS has halted acceptance of proposals until 2016.

BPS has decided to undergo a self-study to review and facilitate the development of cutting-edge recertification that includes traditional elements as well as new activities for all board-certified pharmacists. During this self-study process, they are closing the request for proposals for any new recertification programs. Although we are extremely disappointed that we were not able to submit our proposal to BPS for a HOPA-sponsored BCOP recertification program, we are excited to have an opportunity to participate in the self-study and reshape future recertification activities. We also stand poised and ready to submit a new proposal when BPS reopens the request for proposals. In the meantime, we will continue to collaborate with ACCP and ASHP to offer 6 hours of live continuing education BCOP credits at the HOPA Annual Conference, the ACCP Annual Meeting, and the ASHP Midyear Meeting.

HOPA and Social Media

Although HOPA is well known among most oncology pharmacists, our organization is still relatively young and not as well known outside of our profession. We have taken steps to enhance awareness of our organization through our health policy advocacy efforts (see the HOPA Health Policy Agenda on our health policy website page and the article in this issue of the newsletter about HOPA's first Capitol Hill visits). During the next several months, we will continue to expand the public's awareness of our organization by launching Facebook and LinkedIn pages. These pages will provide HOPA greater visibility to the public and an additional forum for our members to communicate and learn about HOPA events, programming, and efforts. Stay tuned to the HOPA member e-mail updates and the HOPA website for more information about our Facebook and LinkedIn pages. Once these social media forums are up and running, HOPA will launch a Twitter account.

HOPA Urges CMS to Reconsider Aprepitant (Emend®) Reimbursement Policy

In early October the Centers for Medicare & Medicaid Services (CMS) initiated a review reconsidering their aprepitant (Emend®) reimbursement policy. Currently CMS only reimburses oral aprepitant when used as part of an all-oral, three-drug combination (aprepitant, dexamethasone, and 5-HT3 antagonist) used to prevent complications associated with highly emetogenic chemotherapy (i.e., nausea, vomiting). CMS is now reviewing the evidence for using oral aprepitant for moderately emetogenic chemotherapy in combination with dexamethasone and a 5-HT3 antagonist.

Not only did HOPA write a letter in support of the reimbursement reconsideration, but the HOPA Health Policy Committee also encouraged members to comment on this important reimbursement issue. In general, the more comments received, the more likely CMS is to make a policy change. Although the turnaround time for posting comments was short, more than 30 HOPA members responded. We thank each of these members for taking the time to post a comment supporting the reconsideration of the current reimbursement policy, which affects not only institutions but our patients as well. As we continue to grow our advocacy program, we will introduce easy-to-use tools and provide some education about becoming an active participant in our advocacy efforts. We hope that you will participate so that together we can make a difference in the lives of our patients.

Ziv-Aflibercept (Zaltrap®)

Class: Vascular endothelial growth factor (VEGF) inhibitor

Indication: For use in combination with 5-fluorouracil (5-FU), leucovorin, and irinotecan (FOLFIRI) for patients with metastatic colorectal cancer that is resistant or has progressed after receiving an oxaliplatin-containing regimen

Dose: 4 mg/kg every 2 weeks in combination with FOLFIRI

Dose modification: Modify or hold doses based on toxicity.

Common adverse effects: Leukopenia, diarrhea, neutropenia, proteinuria, aspartate aminotransferase/alanine aminotransferase increase, stomatitis, fatigue, thrombocytopenia, hypertension, weight decrease, decreased appetite, epistaxis, abdominal pain, dysphonia, serum creatinine increase, and headache

Serious adverse effects: Hemorrhage, gastrointestinal perforation, compromised wound healing, fistula formation, hypertension, arterial thromboembolic events, proteinuria, neutropenia and neutropenic complications, diarrhea and dehydration, and reversible posterior leukoencephalopathy syndrome

Drug interactions: No dedicated drug-drug interaction studies have been conducted. No clinically important pharmacokinetic drug-drug interactions were found between ziv-aflibercept and irinotecan or 5-FU.

Newly Approved VEGF Inhibitor for Metastatic Colorectal Cancer

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Colorectal cancer is the third most common cancer in both men and women, with an estimated 143,460 new cases and 51,690 deaths in the United States in 2012.[1] It is the third most common cause of cancer death, accounting for 9% of all cancer deaths.[1] Approximately 50%–60% of patients diagnosed with colorectal cancer will develop metastatic disease.[2] Although there are multiple therapy options for metastatic colorectal cancer (mCRC), first-line therapy is generally recognized as fluorouracil and leucovorin with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI).[2] In 2004 bevacizumab became the first available inhibitor of vascular endothelial growth factor A (VEGF-A), a member of the larger VEGF family that is essential for proliferation, growth, and angiogensis.[3,4] The addition of bevacizumab has been shown to increase survival of patients with mCRC when added to FOLFOX or FOLFIRI regimens, granting it U.S. Food and Drug Administration (FDA) approval for use in conjunction with fluorouracil-based regimens for first-line treatment of mCRC.[5,6] Eight years later, ziv-aflibercept received FDA approval on August 3, 2012, for use in combination with FOLFIRI as part of second-line treatment in patients with refractory or resistant mCRC after receiving an oxaliplatin-containing regimen.[7]

Unlike bevacizumab, a human monoclonal antibody that binds VEGF-A, ziv-aflibercept is a fully human, soluble, recombinant fusion protein composed of the extracellular domains of VEGF receptor 1 (VEGFR1) and VEGF receptor 2 (VEGFR2).[4,8] Ziv-aflibercept acts as a receptor decoy with affinity for VEGF-A, VEGF-B, and placental growth factor (PlGF), preventing their ability to activate endogenous VEGF receptors and effectively halting tumor-mediated angiogenesis.[4,8] Currently, multiple studies are being conducted with other cancers such as thyroid, kidney, ovarian, small and non-small cell lung cancer, prostate, non-Hodgkin's lymphoma, breast, melanoma, and pancreatic to evaluate the potential clinical benefit of ziv-aflibercept beyond colorectal cancer.[4,9] Of note, a formulation of aflibercept, marketed as Eylea®, was approved by the FDA in 2011 and is available as an intravitreal injection for the treatment of neovascular age-related macular degeneration and macular edema following central retinal vein occlusion.[10]

In the pivotal, multinational, phase 3 VELOUR trial, 1,226 patients with mCRC who had relapsed on a previous oxaliplatin-based regimen were randomized to receive either ziv-aflibercept 4 mg/kg or placebo on Day 1 every 2 weeks, followed immediately by the FOLFIRI regimen (irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, fluorouracil 400 mg/m^2 bolus, then 2,400 mg/m^2 continuous infusion).[11] Patients were stratified according to Eastern Cooperative Oncology Group (ECOG) performance status and prior therapy with bevacizumab; 30.4% of patients had previously received bevacizumab. After a median follow-up of 22.28 months, the primary endpoint of overall survival (OS) significantly favored ziv-aflibercept with a median survival of 13.5 months versus 12.06 months in the placebo arm and a hazard ratio (HR) of 0.817 (95.34% CI, 0.713 to 0.937; p = .0032). The 2-year survival rates were 28% and 18.7% for ziv-aflibercept and placebo, respectively. The efficacy benefits of ziv-aflibercept remained consistent in analyses of prespecified subgroups of performance status and prior bevacizumab use, as well as other baseline characteristics. The addition of ziv-aflibercept increased median progression-free survival (PFS) to 6.9 months from 4.7 months in the placebo arm (HR 0.758; 95% CI, 0.661 to 0.869; p < .0001). Subgroup analyses of PFS also exhibited consistent, robust results supporting ziv-aflibercept over the placebo arm. The response rate was significantly higher in the ziv-aflibercept arm when compared with the placebo arm (19.8% versus 11.1%; p < .001). A higher incidence of grade 3 and 4 adverse events was reported with ziv-aflibercept compared with the placebo arm, including hypertension, hemorrhage (2.9% versus 1.7%), arterial thromboembolic events (1.8% versus 0.5%), venous thromboembolic events (7.9% versus 6.3%), and proteinuria (7.9% versus 1.2%). Some adverse effects commonly associated with FOLOFIRI treatment were also increased in the ziv-aflibercept arm compared with the placebo arm, including grade 3 and 4 diarrhea, asthenic conditions, infections, palmar-plantar erythrodysesthesia, grade 3 and 4 neutropenia,

thrombocytopenia, and neutropenic complications. The authors concluded that the combination of ziv-aflibercept with FOLFIRI may provide a new therapeutic option for the treatment of mCRC in patients with progressive disease after prior therapy with an oxaliplatin-based regimen.

Ziv-aflibercept binds with greater affinity for VEGF-A than bevacizumab; however, the safety profile remains similar between the two agents, including black box warnings for risk of hemorrhage, gastrointestinal perforation, and compromised wound healing.[3,7,12,13] It is recommended that ziv-aflibercept be temporarily suspended at least 4 weeks prior to elective surgery.[7] The most common side effects (>20%) include leukopenia, diarrhea, neutropenia, proteinuria, aspartate aminotransferase increase, stomatitis, fatigue, thrombocytopenia, alanine aminotransferase increase, hypertension, weight decrease, appetite decrease, epistaxis, abdominal pain, dysphonia, serum creatinine increase, and headache.[7] Adverse effects resulting in discontinuation occurred in 26.6% of patients treated with ziv-aflibercept compared with 12.1% treated with placebo in the VELOUR study.[11]

Ziv-aflibercept is available in a 25-mg/ml concentration as either 100 mg/4 ml or 200 mg/8 ml single-use vials.[7] The recommended dose for ziv-aflibercept is a 4-mg/kg intravenous infusion over 1 hour every 2 weeks, administered prior to FOLFIRI on the day of therapy. The drug should be administered through a 0.2-micron polyethersulfone filter and it should not be combined with other drugs in either the same infusion bag or intravenous line. Ziv-aflibercept should be discontinued if severe hemorrhage, gastrointestinal perforation, compromised wound healing, fistula formation, hypertensive crisis or hypertensive encephalopathy, arterial thromboembolic events, reversible posterior leukoencephalopathy syndrome, nephritic syndrome, or thrombotic microangiopathy is observed. In the event of recurrent or severe hypertension, ziv-aflibercept should be held until the blood pressure is controlled, then resumed at 2 mg/kg for the remainder of therapy. If patients develop proteinuria ≥2 grams per 24 hours, it is recommended to stop therapy until proteinuria is <2 grams per 24 hours. If proteinuria is recurrent, patients should be restarted at 2 mg/kg for the remainder of therapy.

Based on current results, the addition of ziv-aflibercept to FOLFIRI has demonstrated a survival benefit in patients with mCRC previously treated with an oxaliplatin-based regimen; however, this benefit comes at the expense of increased adverse events when compared with FOLFIRI alone. Further evaluation of ziv-aflibercept is warranted to determine long-term benefits and whether it will become the preferred second-line therapy over bevacizumab in patients with mCRC.

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Liposomal Vincristine (Marqibo)

Class: Vinca alkaloid

Indication: Philadelphia chromosome–negative acute lymphoblastic leukemia after two or more relapses or after progression following two or more antileukemia therapies

Dose: 2.25 mg/m^2 intravenously over 1 hour weekly

Dose modifications: Modify or hold doses based on peripheral neuropathy.

Common adverse effects: Constipation, nausea, pyrexia, fatigue, peripheral neuropathy, febrile neutropenia, diarrhea, anemia, decreased appetite, insomnia

Serious adverse effects: Febrile neutropenia, hypotension, respiratory distress, cardiac arrest

Drug interactions: Use with P-glycoprotein inhibitors/inducers and CYP3A inhibitors/inducers should be avoided. Expected to interact with drugs known to interact with nonliposomal vincristine sulfate.

Liposomal Vincristine Approved to Treat Rare Leukemia

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According to the National Cancer Institute, it is estimated that 6,050 adults will be diagnosed with acute lymphoblastic leukemia (ALL) and 1,440 will die from this disease in 2012.[1] Patients who require salvage treatment for recurrent or refractory ALL usually have poor outcomes, with complete response (CR) rates of about 20%–30% and a median survival range of 2–6 months.[2,3] Newer treatment agents are needed to reduce the recurrence rate after first-line therapy.[2] On August 9, 2012, the U.S. Food and Drug Administration (FDA) approved Marqibo (liposomal vincristine) under the accelerated approval program as a treatment option for patients with Philadelphia chromosome–negative (Ph-) ALL who have relapsed two or more times or who have progressed following two or more regimens of antileukemia therapy.[1] Liposomal vincristine consists of vincristine sulfate encased within an aqueous core of sphingomyelin-based liposomes. This formulation was created to facilitate high-concentration targeted drug delivery, reduce toxicities, and create predictable first-order, continuous drug-release kinetics.[2] Vincristine sulfate is a previously approved chemotherapy agent that has been used in many different types of cancer, including leukemias. Vincristine damages the cancer cells through its effect on microtubules, inhibiting mitosis.[4]

A phase 1–2, open-label, multicenter, standard dose-escalation study (VSLI-06) enrolled 36 patients with relapsed or refractory ALL. The subjects received weekly intravenous liposomal vincristine infused over 1 hour at 1.5 mg/m^2, 1.825 mg/m^2, 2 mg/m^2, 2.25 mg/m^2, or 2.4 mg/m^2 with pulse dexamethasone 40 mg orally or intravenously given on Days 1–4 and Days 11–14 of each 28-day cycle. Determination of the maximum tolerated dose and evaluation of antileukemic activity were the major study objectives. All of the subjects were previously treated with nonliposomal vincristine. The maximum tolerated dose was determined to be 2.25 mg/m^2, with the most common toxicities being peripheral neuropathy and constipation. CR was achieved by seven of 36 patients (19%). Of the seven responders, four patients proceeded to an allogeneic stem cell transplantation, achieving CR.[5]

The accelerated approval of liposomal vincristine was based on several phase 1 and 2 studies evaluating its place in the treatment of Ph- ALL.[1] Liposomal vincristine was studied in an open-label, multicenter, single-arm phase 2 study (HBS407) designed to evaluate the safety, tolerability, and effectiveness of reducing the growth of ALL in patients with second relapse or ALL that has returned after two different chemotherapy treatments. The study enrolled 65 patients who received at least one dose of liposomal vincristine. Patients included in the study had a prior response to at least one antileukemia therapy, with a leukemia-free interval of ≥3 months. Patients with Burkitt's lymphoma were excluded, and concomitant corticosteroids were not permitted after Day 5 of therapy. Among the subjects, 46% received liposomal vincristine as fourth-line or greater therapy. Liposomal vincristine was given at 2.25 mg/m^2 intravenously over 1 hour every 7 days. The overall response rate was 35% in very heavily pretreated patients with ALL.[4] Of the 65 patients enrolled, 10 patients (15.4%) responded with either a CR (3/10; 4.6%) or a CR with incomplete blood count recovery (7/10; 10.8%).[1] For the 10 patients with no response, the median duration of remission was 28 days. The median time to the first event of relapse, death, or next therapy was 56 days.[1] The median CR/CR1 duration was 5.3 months and median overall survival was 4.6 months when all 65 enrolled patients were included. The adverse effects were predictable, being similar to those found with nonliposomal vincristine.[4]

To date, no new or unexpected toxicities have been observed with liposomal vincristine administration either in nonclinical studies or clinical experience. There is no clinical evidence that the increased vincristine exposure provided by liposomal vincristine resulted in any increase in vincristine-related adverse effects.[6] The safety of liposomal vincristine was evaluated in two single-arm trials of 83 patients. Serious adverse effects such as febrile neutropenia, hypotension, respiratory distress, and cardiac arrest occurred in 76% of the studies' patients.[1] The most common adverse effects occurring with the 2.25-mg/m^2 dosage were constipation (56.6%), nausea (51.8%), pyrexia (42.2%), fatigue (34.9%), peripheral neuropathy (37.3%), decreased appetite (36.1%), febrile neutropenia (36.1%), diarrhea (34.9%), and anemia (30.1%).[6]

In a repeat-dose comparative toxicology study in rats, liposomal vincristine or nonliposomal vincristine were administered intravenously weekly for 6 weeks. Clinical signs of toxicity consistent with neurotoxicity were greater with liposomal vincristine than with nonliposomal vincristine at equal vincristine sulfate doses of 2 mg/m^2/week. The toxicities observed were uncoordinated movements, weakness, reduced

muscle tone, and limited usage of limbs. Neurological testing indicated drug-induced peripheral neurotoxicity with both drugs. Based on histopathologic examination after 6 weekly doses, liposomal vincristine induced greater peripheral neurotoxicity (nerve fiber degeneration) and secondary skeletal muscle atrophy than the equal dose of nonliposomal vincristine.[7]

Vincristine sulfate is excreted primarily by the liver. A study evaluated the pharmacokinetics of liposomal vincristine in subjects with melanoma who had impaired hepatic function. The dose-adjusted maximum plasma concentration and area under the concentration time curve in patients with moderate hepatic impairment was comparable to patients with normal hepatic function.[8]

Liposomal vincristine is contraindicated in patients with demyelinating conditions. Patients with preexisting severe neuropathy should only be treated after a careful risk-benefit assessment. Dosing or scheduling modifications are needed in patients presenting with peripheral neuropathy. If the patient develops grade 3 neuropathy according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 or persistent grade 2 peripheral neuropathy, then the administration of liposomal vincristine should be interrupted. If peripheral neuropathy remains at grade 3 or increases to grade 4, then liposomal vincristine should be discontinued. If it recovers to grade 2 or 1, then a dose reduction to 2 mg/m^2 is needed. If the patient has persistent grade 2 peripheral neuropathy after the first dose reduction to 2 mg/m^2, then interrupt liposomal vincristine for up to 7 days. If peripheral neuropathy increases to grade 3 or 4, then liposomal vincristine should be discontinued. If it recovers to grade 1, then an additional dose reduction to 1.825 mg/m^2 is needed. If the patient has persistent grade 2 peripheral neuropathy after the second dose reduction to 1.825 mg/m^2, then interrupt liposomal vincristine for up to 7 days. If peripheral neuropathy increases to grade 3 or 4, then liposomal vincristine should be discontinued. If it recovers to grade 1, then an additional dose reduction to 1.5 mg/m^2 is needed.[7]

Liposomal vincristine has a marked dose intensity compared with standard vincristine dosing. The dose intensification results from both a larger milligram dose per unit of body surface area (2.25 mg/m^2 versus 1.4 mg/m^2) and elimination of the need for the dose capping that is routinely applied to standard vincristine.[3] The net results are individual (2–3-fold increase) and cumulative (up to a 10-fold increase) vincristine dose increases.[3]

The plasma pharmacokinetics of liposomal vincristine were investigated in 13 adult patients with relapsed ALL who received liposomal vincristine 2.25 mg/m^2 intravenously over 1 hour. The vincristine sulfate levels reported demonstrate that liposomal vincristine may not be immediately bioavailable and may not be directly comparable to plasma levels of vincristine sulfate after administration of nonliposomal vincristine, which is immediately bioavailable. In a tissue distribution study in rats, administration of 2 mg/m^2 of intravenous liposomal or nonliposomal vincristine showed greater accumulation of vincristine sulfate in sciatic and tibial nerves (as well as the lymph nodes, spleen, and bone marrow) following liposomal vincristine.[7]

The plasma clearance of liposomal vincristine is slow, 345 mL/hr, at a dose of 2.25 mg/m^2. This is in comparison to the rapid clearance of nonliposomal vincristine at 189 mL/min/m^2 (11,340 mL/hr). The slow clearance of liposomal vincristine contributes to a much higher area under the curve for liposomal vincristine relative to nonliposomal vincristine. Following intravenous administration of liposomal vincristine, urinary excretion was a minor route of elimination for vincristine sulfate and its metabolite. Less than 8% of the administered liposomal vincristine dose was eliminated in urine over a 96-hour observation period, which is similar to the urinary excretion of nonliposomal vincristine. Following nonliposomal vincristine sulfate infusion, the main route of vincristine sulfate excretion was the fecal route, accounting for 69% of the administered dose over 72 hours.[7]

Liposomal vincristine is expected to interact with drugs known to interact with nonliposomal vincristine. Nonliposomal vincristine is a substrate for cytochrome P450 3A isozymes, and concomitant use of strong CYP3A inhibitors and inducers should be avoided. Nonliposomal vincristine is also a substrate for P-glycoprotein; therefore, concomitant administration with P-glycoprotein inhibitors and inducers might alter the pharmacokinetics of liposomal vincristine. Liposomal vincristine should only be administered as an intravenous infusion and never administered intrathecally.[7]

Liposomal vincristine is prepared from the Marqibo kit and takes approximately 60 to 90 minutes to prepare. Each single-dose vial contains 5 mg/31 mL (0.16 mg/mL) of vincristine sulfate. A water bath must be used with a calibrated thermometer to maintain a temperature of 63 °C to 67 °C. Using a sterile 0.2-micron filter, withdraw 1 mL of sphingomyelin/cholesterol liposome injection and inject it into the sodium phosphate injection vial. Withdraw 5 mL of vincristine sulfate and add it into the sodium phosphate injection vial and invert the vial five times to mix. Place this vial with a flotation ring around the neck of the vial into the water bath for 10 minutes. After 10 minutes, remove the vial and invert five additional times. Allow this constituted vial to equilibrate for at least 30 minutes at room temperature. The liposomal vincristine should be diluted in 5% dextrose or 0.9% sodium chloride to a final volume of 100 mL. After the final preparation is made, it is stable for 12 hours at room temperature.[7]

Patients should report any burning or local irritation during or after the infusion due to the risk of extravasation. Patients should be advised how to avoid constipation by having a diet high in bulk fiber, fruits, and vegetables; ensuring adequate fluid intake; and using a stool softener such as docusate. Instruct patients to seek medical advice if they experience symptoms of constipation such as bowel movement infrequency, abdominal pain, bloating, diarrhea, nausea, or vomiting. Patients should contact their physician if they experience new or worsening symptoms of peripheral neuropathy such as tingling, numbness, pain, a burning feeling in the feet or hands, or weakness in the feet or hands. Females of reproductive potential should use effective contraceptive measures to prevent pregnancy during treatment and avoid breast-feeding.[7]

Many additional phase 1, 2, and 3 studies are currently enrolling both adults and children to receive liposomal vincristine. The National Cancer Institute is conducting a phase 1 trial in children and adolescents with refractory or relapsed cancers.[3] Liposomal vincristine will also be studied as a first-line therapy for adults ≥60 years old with ALL in a phase 3 study.[6] MD Anderson Cancer Center is conducting a phase 2 study that substitutes liposomal vincristine for standard vincristine in the Hyper-CVAD regimen to create a new regimen, Hyper-CMAD.[3]

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