



Biosimilars and Their Uncertain Future

*Connie Cheng, PharmD
PGY2 Hematology/Oncology Pharmacy Resident
Cleveland Clinic
Cleveland, OH*



Due to increasing advances in biotechnology and generic erosion of branded sales, more pharmaceutical companies are focusing their product development programs on high-value biologic drugs. However, a number of major biologics are currently off patent or will be off patent in the next decade, including hematopoietic growth factors, monoclonal antibodies, and interferons. The anticipated patent expirations of these expensive medicines have prompted the pharmaceutical industry to develop alternative versions of biologic agents, also known as biosimilars. Unlike a small-molecule generic, in which the active substance matches the reference product, biosimilars are not identical to a reference biopharmaceutical drug. During the manufacturing process, characteristics of biopharmaceuticals cannot be replicated, so biosimilars cannot be deemed generic versions of licensed originator biological products.¹ Because of the increasing number of biologic medicines that recently have been approved during the past decade, the growth potential for biosimilars in the global market, especially in the oncology setting, is promising for commercial success. Despite their anticipated cost savings, biosimilars also inevitably will pose challenges for pharmaceutical firms in meeting U.S. Food and

Drug Administration (FDA) regulations throughout their clinical development process. In addition, healthcare providers will face numerous challenges regarding the use of such agents in the practice setting because of limited clinical evidence available to assess and compare their efficacy and safety.

Biological products are currently used to treat a number of disease states, most commonly immunology, endocrinology, hematology, and oncology. They include various classes of products such as monoclonal antibodies, gene therapies, blood components, recombinant proteins, and vaccines. Unlike small-molecule drugs that are synthesized through chemical processes, biological products are derived from human or animal materials. They are highly sensitive to manufacturing changes and present major production challenges in terms of their formulation, purity, and storage. In addition, the molecular structure of biological products is generally characterized as being larger in size and more complex, which renders them virtually irreproducible during the manufacturing process. As a result, the regulatory pathway for development and approval of biosimilars presents scientific and technical challenges. In 2010 the FDA developed an abbreviated approval pathway



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Send administrative correspondence or letters to the editor to HOPA, 8735 W. Higgins Road, Suite 300, Chicago, IL 60631, fax 847.375.6497, e-mail info@hoparx.org. *HOPA News* is published by the Hematology/Oncology Pharmacy Association.

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for biosimilars under Title VII section 351(k) of the Patient Protection and Affordable Care Act (PPACA). The PPACA includes the Biologics Price Competition and Innovation Act (BPCI), which amended the Public Health Service Act (PHSA) to create a new approval pathway that enables introduction of biological products to the U.S. market based on evidence that they are highly similar or “biosimilar” to an FDA-approved biological product, also known as the reference product.² According to the BPCI Act, *biosimilar* or *biosimilarity* is formally defined as “the biological product [that] is highly similar to the reference product notwithstanding minor differences in clinically inactive components,” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product (see **Table 1**).” Currently, the FDA recommends sponsors use a comparability method to demonstrate similarity. The approach must demonstrate that the proposed product has comparable quality, safety, and efficacy as well as a structure that is highly analogous to its reference product via robust analytical characterization. Biosimilars differ from me-too and noninnovator (i.e., copy) biological products in that any minor differences that exist between the biosimilar and reference products are deemed not clinically meaningful. On the other hand, me-too and noninnovator biological products are developed separately, but may or may not have been directly compared to a licensed reference biological drug.³

Regulatory Pathway

To date, the FDA has published three draft guidance documents that outline primary quality, scientific, and regulatory factors considered upon submission of licensing applications for biosimilars. To demonstrate biosimilarity, the FDA recommends using a stepwise approach to compare the proposed biosimilar to its innovator or reference product, which is described in the FDA guidance document, “Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.” The process begins by comparing structural and functional characteristics of the proposed product and reference product using state-of-the-art technology to assess biologic activities and physiochemical properties. The sponsor should then utilize animal data to assess toxicity before comparing clinically relevant pharmacokinetic and pharmacodynamic data between the two products in humans. Because these agents are biologic in nature, they are associated with an increased risk for inducing human immune responses. Thus, the FDA also recommends evaluating clinical immunogenicity, including development of neutralizing and binding antibodies to the drug product.⁴ If the incidence of immunogenicity is low, such studies may also pose logistical challenges for sponsors, such as subject enrollment if a large sample size is required.⁵ If any uncertainties regarding the biosimilarity, especially regarding safety, purity, and potency, of the two products remain after performing these steps, the sponsor should consider conducting clinical studies to further evaluate safety and effectiveness of the proposed product.⁴ Because biological products are unique and complex, there are numerous factors that impact biosimilarity. Despite the existence of guidance documents from the FDA, a well-defined approval pathway for biosimilars is lacking for industry stakeholders. Therefore, development programs for biosimilars currently are evaluated by the FDA on a case-by-case basis.

Biosimilar Opportunities

During the past decade, biological products, especially monoclonal antibodies, have proven to be the most lucrative and primary drivers in generating significant revenue for the pharmaceutical industry, with expected total global sales to reach \$252 billion in 2017.⁶ The biologics market offers a tremendous opportunity for developers of biosimilars as the global incidence and prevalence of cancer continues to increase. Furthermore, therapeutic successes of various targeted biological therapies already have been demonstrated and documented.⁵ The number of patents for highly priced branded biologics are scheduled to expire during the next decade and some have already expired; more companies are looking to enter the biosimilars market with a number of therapeutic areas offering growth opportunities, especially oncology. In the setting of healthcare reform, there is an increased need for more cost-effective treatments, particularly as personalized medicine continues to expand along with the growing use of biologics and targeted treatment in oncology. Currently, biosimilar versions of three biological products—somatropin, epoetin, and filgrastim—are marketed in Europe. To date, no biosimilar has

been launched in the United States but there have been three biological products approved by the FDA that are considered biosimilars in other regulated markets. These include Tev-Tropin[®] and Omnitrope[®]—whose reference product is Genotropin[®]—and, most recently in September 2012, Tbo-Filgrastim[®]—whose reference product is Neupogen[®]. All of these products gained FDA approval in the United States via the full biologics license application (BLA) rather than a 351(k) biosimilar application because the abbreviated approval pathway had not been established by the FDA at the time of submission.^{7,8} In addition, Teva, the sponsor of Tbo-Filgrastim[®], filed a BLA rather than a 351(k) biosimilar application because biological products are allotted a prolonged market exclusivity compared with biosimilars. However, Tbo-Filgrastim[®] is not scheduled for a U.S. market launch until November 2013 due to a patent infringement lawsuit filed by Amgen, the sponsor for Neupogen[®].⁸ This highlights one of several anticipated issues surrounding FDA approval of future biosimilars via the abbreviated pathway.

Biosimilar Challenges

Brand loyalty, greater immunogenicity concerns, lack of automatic therapeutic substitution (i.e., switch to an AB-rated generic drug), substantial research and development expenses, lack of well-defined biosimilar approval pathways, and competition from second-generation branded biologics are all potential factors limiting biosimilar uptake in the developed markets, including the United States, the European Union, and Japan.⁷ Numerous barriers remain for biosimilars to achieve market access despite various efforts to help drive biosimilar uptake, such as the FDA's introduction of an abbreviated approval pathway, an increase in the use of biological products, and the need for more cost-effective treatments. Although the development process of biosimilars is longer and more expensive than for generics (which typically take 3 to 4 years to develop at a cost of \$5 to \$10 million), biosimilar development is much shorter and less costly than that of branded biological products, which can take on average 8 years, approximately 2 to 4 years less than that of a branded biologic drug.⁹ For instance, Sandoz, an established leader in the European Union's

biosimilar market, reports that the cost of biosimilar development can range from \$75 million to \$250 million compared with the \$2 million to \$3 million needed to develop small-molecule bioequivalent drugs, primarily driven by the enormous cost of building manufacturing plants for biosimilar production. However, the cost of biosimilars remains significantly less than that of their branded biological counterparts, which is approximately \$800 million.¹⁰ Clinical trials may also require a large subject enrollment number to prove efficacy and safety of biosimilars. Few companies can afford to enter the biosimilars market, and currently there are a limited number of countries and sites highly experienced in biosimilar trials with well-developed biologic manufacturing facilities. In addition, a majority of patients in emerging economies or developing countries pay for their medications out of pocket, making affordability a major issue for biosimilar manufacturers.⁹

Future Implications

Numerous controversies and questions remain regarding the regulation and clinical application of biosimilars. Currently, the BPCI Act grants approved BLAs 12 years of market exclusivity, which means no application submitted via abbreviated approval pathway for biosimilars can be approved until a minimum of 12 years has passed following approval of the reference product. Furthermore, the sponsor for proposed biosimilars must wait at least 4 years to initially submit the licensing application following approval of the reference product.⁷ Because patent protection for small-molecule drugs is primarily focused on drug composition, an area of debate in development of biological products is the data protection period, specifically determining whether biological products may require more patents relating to complex manufacturing processes. Due to the lack of a clearly defined approval pathway for biosimilars and limited information provided in the FDA's guidance documents for demonstrating biosimilarity, the definition and standard for testing biosimilarity will likely change over time.¹¹ In the United States, an area of particular concern for clinicians is that biosimilars do not receive automatic substitution like AB-rated generic drugs⁷ because therapeutic equivalence must be established for two products to be considered interchangeable. In other words, generic

Table 1. Characteristic Differences Between Generic Drugs and Biosimilars^{4,13,14}

	Generic Drugs	Biosimilars
Definition	<p>Bioequivalent to an approved brand drug</p> <p><i>Bioequivalence</i> is defined as the relationship between the brand drug and the generic drug. One way bioequivalence is measured is by evaluating the time it takes the generic drug to reach the bloodstream in 24–36 healthy, normal volunteers. This determines the rate and extent of absorption—or bioavailability—of the generic drug, which is then compared with that of the brand (reference product). The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the brand drug.</p>	<p>Biological products that are highly similar to the reference product</p> <p>There are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency. They must have the same mechanism of action, condition(s) of use, route of administration, dosage form, and strength.</p>
Regulatory Law	Hatch-Waxman Act of 1984 of the Food, Drug, and Cosmetic Act	Biologics Price Competition and Innovation Act of the Public Health Service Act of 2009
Approval Process	Abbreviated New Drug Application (ANDA)—505 (i) application	351 (k) application

and reference products are deemed therapeutically equivalent due to their identical chemical composition and bioequivalence. Although biosimilars have comparable safety and efficacy, they are not identical to their reference products and therefore cannot guarantee therapeutic equivalence. Inherent differences among biosimilars also make extrapolation of clinical data across multiple therapeutic indications difficult because risk-to-benefit ratios may vary among different patient populations. Potential clinical differences, including effectiveness and safety signals, may not be detected until after approval. As a result, the FDA recommends making decisions to use biosimilars in the clinical setting on an individual basis.¹

Conclusion

As an increasing number of biosimilar markets become established globally, more competition is inevitable due to the promising commercial and financial opportunities offered. Because more biosimilars are forecasted to enter the U.S. market during the next decade, it is important that institutions, including the pharmacy and therapeutics committees established within hospitals and hospital systems, use formalized and standardized processes to evaluate individual biosimilars and develop policies to guide their use within the appropriate patient populations.¹² Due to the limited clinical evidence currently available for biosimilars, maintaining pharmacovigilance and conducting robust postmarketing safety monitoring will also be essential to ensuring appropriate use of these biological products over time. 

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HOPA Member Participates in Hill Day for Oral Chemo Parity

Jordan Wildermuth, HOPA Health Policy & Advocacy Manager

On July 18, 2013, eleven activists from the cancer and pharmacy communities, including HOPA representative Sarah Hudson-DiSalle, PharmD, converged on Congress to solicit support for oral chemotherapy parity legislation (H.R. 1801—The Cancer Drug Coverage Parity Act). The Hill Day was sponsored by the Patient Equal Action Coalition (PEAC)—a patient-focused coalition of organizations representing patients, healthcare professionals, care centers, and industry, advocating to ensure that cancer patients have equal access to all approved anticancer regimens—to educate Senate HELP Committee Members as well as Senators from states that have passed parity legislation about the need for federal legislation in the Senate.

The goal of the meetings was to identify a republican Senator to co-sponsor a companion bill to the Drug Coverage Parity Act with Senator Al Franken (D-MN). The group visited with the offices of Senators Rand Paul (R-KY), Roy Blunt (R-MO), Jim Inhofe (R-OK), John Cornyn (R-TX), Tim Scott (R-SC), Pat Roberts (R-KS), Rob Portman (R-OH), Marco Rubio (R-FL), Mike Enzi (R-WY), Ted Cruz (R-TX), Chuck Grassley (R-IA), Lamar Alexander (R-TN), Mike Lee (R-UT), and Orrin Hatch (R-UT).

The advocates were well received and delivered the key messages of parity while helping to dispel misconceptions about the legislation. One argument in opposition to the legislation is the myth that cancer parity is a mandate that requires insurers to cover oral therapies. The proposed legislation applies only to health plans that already cover chemotherapy agents, so it is not a mandate. The most promising interactions from the day were with Senators Portman and Paul, and follow-up discussions were coordinated with HOPA and PEAC. Advocates were active

in communicating progress of the day through social media venues, and Sarah received a lesson in tweeting from her fellow advocates!

Despite the growth in development of oral and intravenous (IV) chemotherapy agents, the systems for medical and pharmacy benefits in the United States have remained relatively static. Insurance covers oral chemotherapy under its pharmacy benefit, unlike IV chemotherapy, which is covered under medical benefits. Under some plans, copayments or coinsurance for oral chemotherapy medicines can run into the hundreds or thousands of dollars every month. At a time when families are struggling with the emotional, physical, and financial burdens that accompany cancer, they shouldn't be distressed about making large, out-of-pocket expenditures to receive lifesaving medication. Chemotherapy parity helps patients access their medications by prohibiting private insurance plans from charging higher out-of-pocket expenses than for IV-infused medications. There currently are no approved parity statutes at the national level that impact the Employee Retirement Income Security Act (ERISA), which governs self-insured health benefit plans.

Take Action

Pharmacists who want to help improve patient care and change this disparate practice can contact their representatives and ask them to co-sponsor H.R. 1801, the Cancer Drug Coverage Parity Act by visiting HOPA's legislative action center (<https://voterveice.net/HOPA/home>). Individuals who live in Alabama, Illinois, Kentucky, or Ohio should contact their respective senator and ask him or her to introduce a companion bill to H.R. 1801 in the senate. Those senators include Senators Jeff Sessions (R-AL), Mark Kirk (R-IL), Paul, and Portman. 

HOPA Health Policy Committee Member Visits the Hill

Kellie L. Jones, PharmD BCOP FCCP
Clinical Associate Professor
Purdue University College of Pharmacy
West Lafayette, IN

On October 3, 2013, I attended the Ovarian Cancer National Alliance roundtable meeting in Washington, DC, as a representative of the HOPA Health Policy Committee. Prior to the start of the meeting, Erin Morton, HOPA's health policy consultant from Drinker, Biddle & Reath, and I visited the offices of Senator Dan Coats (R-IN) and Representative Susan Brooks (R-IN). During meetings with their staff, I was able to discuss HOPA's goals, my role as an oncology pharmacist, and H.R. 1801, the Cancer Drug Coverage Parity Act. Although the government was shut down at the time, we were still able to have successful meetings and get the health policy message of HOPA out to our policymakers. One of our goals was to obtain support from Representative Brooks's office for H.R. 1801 because currently there are no supporters from Indiana. 



The Resident's Cubicle: Transition to PGY2

Alex Shillingburg, PharmD

Bone Marrow Transplant Clinical Specialist

West Virginia University Healthcare

Morgantown, WV

Welcome to the small corner of the hospital that remains a constant flurry of activity, with long hours and late nights, plenty of sweat and tears, a perpetual stream of productivity, and a learning curve that continues to get steeper and steeper each year. This place, both loved and hated, is known as the Resident's Cubicle. More than simply a physical location, the Resident's Cubicle will be a *HOPA News* recurring feature focusing on issues specific to oncology pharmacy residencies. This column will strive to keep the topics short and sweet and take a more conversational tone than traditional clinical articles.

As the midpoint of the residency year is approaching, the topic selected for this edition concerns the challenges of a second-year (PGY2), compared with a first-year, residency. Coming into a PGY2 oncology residency, most residents have been exposed to the high demands experienced during their first year of residency. Managing the responsibilities associated with various committees, time-intensive rotations, teaching and precepting, projects, formulary management, and staffing expectations is something that residents entering their second year have come to expect; however, this does not always help alleviate stress when the resident is in the thick of it. In addition, there are facets of an oncology PGY2 that can make managing these multiple obligations inherently more difficult.

The first difference that residents may not be prepared for is the increased expectations of a PGY2 resident. The quality of written work, oral presentations, and research projects should be at a higher level during the second year. Residents may expect to continue at the same level of work as a PGY1 resident with a shift in focus to more oncology topics. They should, however, prepare for an increase in intensity, similar to the final push at the end of a long run, to finish strong and come away with the most benefit from the oncology residency experience. Preceptors can assist in this process by acting as practice models and being clear with expectations. Upon completion of the program, the resident will likely step directly into the role of clinical specialist and be expected to produce results at this higher caliber; therefore, their final products should reflect that expectation during the second half of the residency year. Preceptors should provide ample feedback and coaching, but continue to push residents until work is of a quality acceptable for that of a soon-to-be colleague.

Another key difference between PGY1 and PGY2 is the level of independence the resident exhibits. For the same reasons that expectations of quality are higher, those of independent practice should also be higher. Independent practice should not only include rounding independently with the team on a rotation, but should extend to all areas

of practice such as management and operational issues, precepting students, drug information questions, and protocol development. The dedication residents feel toward their patients and the sense of ownership of their care should increase. The distinct lines that exist at the changing of a rotation in the first year are much more blurred during the oncology year. Follow-up in the oncology world spans beyond getting the patient to discharge and home; it includes supportive care as treatment progresses, as diseases relapse and remit, and as chronic complications wax and wane. The responsibility that develops for these patients spans the course of their residency year; residents find themselves personally concerned for the welfare of their patients and following up even after a particular rotation has ended. This characteristic is highly desirable in a resident and in a practitioner but can significantly add to the stress experienced from the already increased workload of a PGY2 resident.

The final difference that I will discuss here is the impromptu mentoring of PGY1 residents or students interested in oncology. A resident can be a very approachable and inspiring mentor for an ambitious student or resident. The role of mentor can be a very rewarding experience for the oncology resident. This is a responsibility that does not come with a title, won't result in any fodder for a CV, and may involve investing a great deal of time with very little to show for it at the end. From a personal and professional satisfaction standpoint, however, mentoring and sharing your passion for the practice of oncology pharmacy can add significant depth and experience to your career. A resident may find themselves taking on extra projects, reviewing articles, and critiquing abstracts for their mentee that can substantially add to their workload.

So, how can a resident avoid becoming overwhelmed? Become a time-management pro and prioritize and reprioritize on a regular basis. Celebrate the small victories, stay motivated, and work hard, but be sure to take time to enjoy family, friends, and extracurriculars. To avoid reaching a breaking point, seek advice and support from mentors and preceptors when you begin to feel overwhelmed. And, try to stay inspired and passionate about your practice. There is a reason that you chose to complete a PGY2 in the field of oncology; don't forget that reason and stay focused on your goal! 

The Resident's Cubicle is a new feature column in HOPA News. If you would like to submit an idea for a future issue, please contact HOPA Senior Managing Editor Rachel Bennett at rbennett@connect2amc.com.

HOPA Fall Oncology Pharmacy Practice Management Meeting Highlights

LeAnne Kennedy, PharmD BCOP CPP

Clinical Specialist

Wake Forest University Baptist Medical Center

Winston Salem, NC

On September 27, more than 160 pharmacists gathered in Chicago for HOPA's 1st Annual Oncology Pharmacy Practice Management Meeting. Seasoned practitioners presented on topics such as expanding clinical services, managing implementation of computerized physician order entry (CPOE) systems, using Smart pumps, and understanding USP 797 updates, reimbursement, cost-containment, biosimilars, and communicating with pharmacy executives. Not only were the presentations very comprehensive and up to date but they also provided time for attendees to ask questions. Attendees were able to discuss challenging subjects and network with presenters and other attendees.

Gene Wetzstein and Ryan Naseman's presentation kicked off the event and discussed the development, justification, and implementation of clinical pharmacy services. They cited decreasing throughput for the hospital as a potential benefit of the service. Wetzstein and Naseman also suggested that decreasing the time from clinic visits to admission to discharge to decrease length of stay also would help administrators justify clinical pharmacy services.

Many institutions have moved or are planning to move to new CPOE systems, so the discussion on planning and managing the CPOE system was very timely. Scott Soefje and Joseph Bubalo provided helpful hints for getting started (test the system, test the system, test the system) and system maintenance (review which protocols are being used and remove those that are not). The use of Smart pumps is another safety measure that many of us are using or beginning to use in our institutions. Erick Borkowski and Wyndie Tse were able to share some of their experiences for getting started and managing their systems, including working together with their nursing counterparts.

Ryan Forrey presented an overview of key topics related to USP 797 and National Institute for Occupational Safety and Health compliance, which was a great review for anyone planning to establish or renovate a pharmacy. During Phil Johnson's discussion, he focused on the importance of learning how to talk with health system administrators and purchasers to improve our reimbursement. He stressed that pharmacists should understand the revenue cycle and the effect Medicare and private pay insurers have on more expensive agents.

We all enjoyed the presentation on cost-containment strategies and challenges for oncology providers. Niesha Griffith shared how her institution helped minimize the cost of expensive therapies by understanding drug shortages and establishing policies for high-cost therapies and off-label use of medications. James Stevenson presented a discussion on biosimilar formulary considerations, which summarized the process of approvals for biosimilars and how these products affect oncology patient care. The session clarified the difference between biosimilars, interchangeable biosimilars, and full Biologics Price Competition and Innovation Act of 2009-approved biologics. The final presentation, from James Jorgenson, provided tools for effective and persuasive communication with the C-suite.

After a long, full day of learning, everyone gathered to discuss key issues affecting their respective institutions. It is fair to say that the meeting was a huge success and one that will be repeated again in the future. If you have suggestions for topics or speakers, the planning committee welcomes your comments; please send them to info@hoparx.org. 

Calling All Photographers...

"Day in the Life of a HOPA Pharmacist"

Photo and Caption Contest

All participants win free extended months membership for each photo submitted (up to 3). Visit hoparx.org for contest details. All photos must be submitted by February 1, 2014.



Board Update

Niesha Griffith, RPh MS FASHP, HOPA President



As I write this column, I find it hard to believe that the holiday season is upon us. This is the perfect time to reflect on all of the people and things we are thankful for. I am fortunate to say that I have much to be thankful for both personally and professionally. My daughter is thriving as a sophomore in college at West Virginia University, my son has managed to turn all of his Cs into As and Bs (after much prodding from his mother!), and my friends, family, and colleagues all are in good health.

This year I am especially thankful for the growth and success of HOPA as an organization. This comes as a result of the hard work and dedication of our committed members and staff. The Fall Oncology Pharmacy Practice Management Meeting was a tremendous success, and plans for a similar meeting next year are already underway. Our health policy activities continue to highlight the important role of hematology/oncology pharmacists and to create opportunities for us to build collaborative relationships with other healthcare providers. The HOPA Research Committee recently awarded a \$25,000 research grant. The Leadership Task Force recommendations were approved during the November Board Meeting, helping to chart the course for building leaders within the organization and the profession. Last, planning for the 10th Anniversary Gala is well underway, and the evening promises to be a memorable one.

Fall Practice Management Meeting

For those of you who had the opportunity to attend this inaugural event, it was hard to ignore the excitement and interest surrounding the educational programming, the Q&A that followed each session, and the networking opportunities during the breaks. The success of the meeting was further validated by the great turnout and favorable evaluations from the 160 attendees.

What was the most memorable aspect of the educational program?

“The speakers were experienced and knowledgeable—true resources! This course was a total homerun.”

“It’s about time we saw some relevant information to practice other than clinical!”

“This was real bread and butter information. Loved it.”

“Great discussions after the presentations. Loved the ability to network and talk to peers at other organizations.”

“The enthusiasm that both participants and speakers had was awesome to have experienced.”

“The accessibility of the presenters and their willingness to engage in further discussion was terrific.”

“There was a wonderful array of helpful information and take-home tasks.”

“Almost all of the presentations were on topics and issues I am currently facing in my practice.”

I want to personally extend a huge expression of gratitude to our speakers, attendees, sponsors, and HOPA staff who helped make this meeting an overwhelming success. Due to the response and interest, we will host next year’s meeting at a similar time and venue in Chicago. Watch for details in an upcoming newsletter.

Health Policy Activities

HOPA’s health policy activities are thriving due to the commitment of our Health Policy Committee members. In October, Kellie Jones attended the Ovarian Cancer National Alliance Advocate Conversations Regulatory & Scientific Session Meeting in Washington, DC. While there, Kellie, accompanied by Erin Morton from Drinker Biddle & Reath (DBR; HOPA’s lobbyist in Washington, DC), also met with staff in the offices of Senator Dan Coats (R-IN) and Congresswoman Susan Brooks (R-IN) to provide an overview of HOPA and our healthcare policy agenda and to urge support for sponsorship of the Cancer Drug Coverage Parity Act.

The three recently created health policy work groups tasked with working on issues related to provider status for pharmacists, access to pain medications for cancer patients, and counterfeit drug prevention have commenced, and we look forward to hearing about their progress.

HOPA was represented by Jeremy Scott from DBR and me at the American College of Clinical Pharmacology (ACCP) Annual Meeting in Albuquerque, NM, during which we participated in their Advocacy Program and Hematology/Oncology PRN Business Meeting. We also were fortunate to meet with ACCP leadership to discuss their advocacy initiative, the Comprehensive Medication Management Benefit. This important proposed legislation aims to seek recognition for the direct patient care services of qualified clinical pharmacists as a covered benefit under the Medicare program by amending the Social Security Act, Section 1861.

Two weeks ago, I had the opportunity to join a team of HOPA members, including Mike Vozniak, Suzanne Simons, Jeremy Scott, and Erin Morton, in Washington, DC, to meet with leadership from the Association of Community Cancer Centers, the American Society of Health-System Pharmacists (ASHP), and the American Pharmacists Association (APhA). During the meetings, we discussed each organization’s advocacy priorities, educational offerings, and potential areas for collaboration.

Provider status initiatives for ASHP and APhA were a large part of our discussions. ASHP and APhA are taking somewhat different approaches than ACCP to seeking recognition for cognitive services provided by pharmacists. They are pursuing provider status for all pharmacists by amending the Social Security Act, Section 1861, and will primarily focus on providing patient care services in medically underserved areas. I encourage you to visit the websites of each of these organizations to learn more. Summaries of our discussions with ACCP, ASHP, and APhA will be shared with the provider status workgroup, who will then provide recommendations on HOPA's next steps related to this advocacy initiative. The subject of provider status/comprehensive medication management will most certainly be a discussion topic during our annual meeting in New Orleans.

HOPA continues to engage its members in the policy process through the use of social media. Members are encouraged to follow @hopaRX on twitter to receive the latest policy updates affecting hematology/oncology pharmacy. We also encourage you to engage with your legislators through social media. Currently, 100% of senators and more than 90% of representatives are on Twitter.

The Health Policy section of the website has been improved to allow for easier navigation by the addition of buttons, inclusion of more concise wording, and clearer organization of the advocacy activities section. There you can find HOPA's health policy agenda, completed issue briefs, comments and letters sent by HOPA, sign-on letters, and a legislative tracker that highlights the progress of cancer care and pharmacy legislation. Please take a moment to visit our website at www.hoparx.org and click on the Healthy Policy and Advocacy tab.

HOPA Foundation Grant Award

We are pleased to announce that the 2013 HOPA research grant recipient is Kerry Parsons, PharmD. She was awarded \$25,000 for her project, "The Identification and Limitation of Pediatric Chemotherapy Errors Associated with the Transition to Computerized Provider Order Entry (CPOE)." Parsons is a pediatric hematology/oncology pharmacist at Children's of Alabama in Birmingham, AL.

Leadership Task Force Recommendations

As I mentioned in my last update, a task force was assembled to explore recommendations to ensure ongoing and capable leadership

for the association and to assist in developing leadership skills within the profession. Recommendations from the task force were approved at the November board meeting and include

- integrating consideration for leadership traits into the candidate application and evaluation process for board and committee positions
- integrating leadership-focused content in educational programming
- incorporating mentorship skills into professional development content
- utilizing expertise of past presidents to provide feedback on the direction and performance of the association
- annually assessing our volunteer work force structure to constantly align with strategic direction, member needs and healthcare environment.

Some of these recommendations will require changes in our by-laws, so expect to see future HOPA communications addressing these important developments for the organization.

10th Anniversary Gala

The planning for this event is in full swing and the evening is shaping up to be a fun and exciting evening! It will be a tremendous opportunity for us to have HOPA's past, current and future leaders together to commemorate our organization's accomplishments and to offer our gratitude to you, our valuable members. There will be something for everyone, whether you are a HOPA founding member or a first-time conference attendee. Please mark your calendars for this special event and watch for more details and updates on HOPA's social media outlets (LinkedIn, Facebook, and Twitter at #HOPARX10Gala.)

Thank you for being a valuable member of HOPA and supporting this great organization. Best wishes to you and your family for a happy, healthy, and safe holiday season.

New HOPA Patient Advocacy Award

Demonstrates leadership and collaboration while advocating for outstanding patient care.

Application Deadline: February 3, 2014.

Winners announced at the HOPA 10th Annual Conference.

Made possible through a generous grant from Teva Oncology

Recalls, Withdrawals, and Safety Alerts from the FDA

Recalls

There have been numerous recalls of compounded sterile products this quarter. The following are a few of those recalls.

Hospira, Inc.

Hospira announced that it initiated a voluntary nationwide recall of one lot of Metoclopramide Injection, USP, 10 mg/2 mL (5 mg/mL), NDC 0409-3414-01, Lot 28-104-DK and two lots of Ondansetron Injection, USP, 4 mg/2 mL, (2 mg/mL), NDC 0409-4755-03, lots 29-484-DK and 29-510-DK. This action is due to a confirmed vial defect where glass particulate matter (glass strands) were identified as being affixed to the inside of the vial walls. There is potential for the glass particulates to dislodge into the solution. www.fda.gov/Safety/Recalls/ucm370658.htm

Beacon Hill Medical Pharmacy

Beacon Hill Medical Pharmacy d/b/a/ Rxtra Solutions (Beacon Hill) in Southfield, MI, is voluntarily recalling all lots of certain sterile products to the user level. There is a question of sterility assurance for the affected products raised by the U.S. Food and Drug Administration (FDA). Please see the online table for a complete list of medications affected. www.fda.gov/Safety/Recalls/ucm363284.htm

Specialty Compounding

Specialty Compounding, LLC, is voluntarily recalling all lots of sterile medications within expiry. Note, an earlier version of this news release indicated that the recall applied to all unexpired sterile compounded products dispensed since May 9, 2013; however, the recall applies to any sterile medication that has not reached its expiration date, including all strengths and dosage forms. The recall was initiated after reports of bacterial infections affecting 15 patients receiving treatment with intravenous calcium gluconate. No calcium gluconate was shipped outside the state of Texas. www.fda.gov/Safety/Recalls/ucm365315.htm

Avella Specialty Pharmacy

Avella Specialty Pharmacy is voluntarily recalling compounded sterile medications. The recall is a result of concerns of sterility assurance with the specialty pharmacy's independent testing laboratory, Front Range Laboratories. Avella is recalling Bevacizumab 1.25 mg/0.05 mL PF with lot 12-20130508@179 and an expiration date of November 3, 2013. www.fda.gov/Safety/Recalls/ucm367703.htm

Leiter's Compounding Pharmacy

Leiter's Compounding Pharmacy is voluntarily recalling lots of its sterile products due to concerns of sterility assurance with Front Range Laboratories, Leiter's compounding pharmacy's independent testing laboratory. The following products and lot numbers are subject to the nationwide recall: Bevacizumab lot 08052013@1, expiry 11/03/13; Bevacizumab lot 08052013@4, expiry 11/03/13. www.fda.gov/Safety/Recalls/ucm368012.htm

Hematology/Oncology Approvals and Safety Notifications

On September 6, 2013, the FDA approved paclitaxel protein-bound particles (albumin-bound; Abraxane), in combination with gemcitabine, for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas. www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm367613.htm

On September 30, 2013, the FDA granted accelerated approval to Perjeta (pertuzumab) as part of a complete treatment regimen for patients with HER-2 positive, locally advanced, inflammatory or early stage, operable breast cancer (neoadjuvant setting). Perjeta is the first FDA-approved drug for the neoadjuvant treatment of breast cancer. www.fda.gov/newsevents/newsroom/pressannouncements/ucm370393.htm

ISMP Medication Safety Alert!

July 11, 2013 (Volume 18, Issue 14): The syringe pull-back method of verifying intravenous (IV) admixtures is unreliable because there is a potential for vials and syringes to be interchanged.

August 8, 2013 (Volume 18, Issue 16): There is a possibility of confusion when using the abbreviation "ltr." It has been interpreted as liter as well as hour, and ISMP is considering adding "ltr" to the list of confusing abbreviations.

September 5, 2013 (Volume 18, Issue 18): www.ismp.org/Newsletters/acutecare/showarticle.asp?id=58

1. There have been numerous reports of vinCRISStine being given intrathecally, leading to death and neurological devastation. ISMP recommends the following practices:
 - Dispense IV vinCRISStine in a minibag of a compatible solution (e.g., 25 mL for pediatric patients and 50 mL for adults) and never dispense or administer the drug using a syringe.
 - Prohibit IV vinCRISStine in areas where intrathecal medications are administered or stored.
 - Confirm that any prescribed intrathecal medications have been administered before dispensing IV vinCRISStine.
2. There have been reports of 10-fold overdoses with toptecan due to decimal points not being seen. ISMP recommends questioning doses greater than 5 mg as well as requiring mg/m² and preprinted order sets.

September 19, 2013 (Volume 18, Issue 19): The ISMP recommends having a hard stop of weekly versus daily for oral and injectable methotrexate for appropriate indications.

Changes in Safety Labeling

July 2013: www.fda.gov/Safety/MedWatch/SafetyInformation/ucm363949.htm

Elspar

Changes to Elspar labeling include the following:

- Glucose intolerance can occur and in some cases is irreversible. Cases of diabetic ketoacidosis have been reported. Monitoring of serum glucose is recommended.
- There have been reports of posterior reversible encephalopathy syndrome (PRES) in some patients treated with Elspar in combination with other agents. Discontinue using Elspar in patients with suspected or diagnosed PRES.
- Medication errors, including under- and overdoses, have occurred with Elspar when different formulations and routes

of administration (IM versus IV) have been interchanged inappropriately. Do not interchange Elspar with Erwinia.

Leuprolide

- Reports of convulsions in patients with a history of seizure, epilepsy, cerebrovascular disorders, central nervous system anomalies, or tumors, and patients taking concomitant medications associated with seizures such as bupropion and selective serotonin reuptake inhibitors, have occurred. Convulsions have also been reported in patients without any of the above mentioned conditions. Patients who experience convulsions while on a GnRH agonist should be managed according to current clinical practice.
- Serious drug-induced liver injury has been reported.

Vemurafenib (Zelboraf)

The following changes have been made to labeling:

- Increased incidence of cutaneous squamous cell carcinoma (cuSCC), keratoacanthoma, and melanoma have been reported. The median time to the first appearance of cuSCC was 7 to 8 weeks; approximately 33% of patients who developed a cuSCC while receiving vemurafenib experienced at least one additional occurrence with median time between occurrences of 6 weeks. Potential risk factors associated with cuSCC observed in clinical studies using vemurafenib included age (≥ 65 years), prior skin cancer, and chronic sun exposure.
- Tumor promotion in BRAF wild-type melanoma has been reported in patients exposed to BRAF inhibitors.
- Abnormalities in liver laboratory results have occurred and the vemurafenib should be reduced or treatment should be interrupted or discontinued if this occurs. Monitoring of transaminases, alkaline phosphatase, and bilirubin should be done prior to initiation and monthly during therapy with vemurafenib.

- The safety and effectiveness of giving vemurafenib with ipilimumab has not been established and grade 3 increases in transaminases and bilirubin have occurred in the majority of patients receiving this combination.

Oxaliplatin (Eloxatin)

Changes in labeling include hypersensitivity and infusion reactions (laryngospasm).

Vandetanib (Capreleso)

Intestinal perforation has occurred in 0.4% of patients treated with vandetanib compared with placebo.

August 2013: www.fda.gov/Safety/MedWatch/SafetyInformation/ucm365214.htm

Doxil (Doxorubicin Liposomal)

Postmarketing experience has shown secondary oral cancers and primary squamous oral cancers have occurred.

September 2013

Rituximab (Rituxan)

FDA-approved changes to the prescribing information of the immune-suppressing and anticancer drugs Arzerra (ofatumumab) and Rituxan (rituximab) to add new Boxed Warning information about the risk of reactivation of hepatitis B virus (HBV) infection. The revised labels also will include additional recommendations for screening, monitoring, and managing patients on these drugs to decrease this risk. www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlerts-forHumanMedicalProducts/ucm369846.htm

Fentanyl Patches

In an effort to minimize the risk of accidental exposure to fentanyl patches, the FDA is requiring the manufacturer of Duragesic to print the name and strength of the drug on the patch in long-lasting ink in a color that is clearly visible to patients and caregivers.

www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlerts-forHumanMedicalProducts/ucm369457.htm

HOPA 10TH ANNUAL CONFERENCE

March 26–29, 2014

Hilton New Orleans Riverside | New Orleans, LA

Registration is open. Visit Conference Web Central for details, time, and session descriptions.

HOPA's Scope of Hematology/Oncology Pharmacy Practice Released

Lisa M. Holle, PharmD BCOP

Assistant Clinical Professor

University of Connecticut School of Pharmacy

Storrs, CT

Laura Michaud, PharmD BCOP

Manager, Clinical Pharmacy Services

The University of Texas MD Anderson Cancer Center

Houston, TX

In 2010, HOPA updated its strategic plan, which included a priority focused on developing HOPA as the source for practice standards to support roles and responsibilities of oncology pharmacists. One objective of that goal area was to increase the understanding of oncology pharmacists' scope of practice across the cancer care continuum. Therefore, the HOPA Board identified and invited ten HOPA members with varying backgrounds, practice sites, and geographical locations to form a task force to develop the scope of practice document, representing the wide spectrum of practices within oncology pharmacy. The

task force was led by Laura Michaud and included Lisa Holle; Lauren DeCloe, PharmD BCOP; Christopher Fausel, PharmD MHA BCOP; Philip Johnson, MS RPh; Susannah Koontz, PharmD BCOP; Karl Kwok, PharmD; Michele Rice, PharmD; and Sol Yoder, PharmD BCOP.

Beginning in October 2011, the task force defined the timeline and methodology for developing this scope of practice document (see **Figure 1**). This document was vetted for veracity on several levels, including peer reviewers Janet Espirito, PharmD BCOP; Amy Hatfield Seung, PharmD BCOP; Lily Leu, PharmD; and Virginia Spadoni,

Figure 1. Timeline and Methodology for Development of Scope of Practice Document



PharmD BCOP; HOPA's Board of Directors; and HOPA membership, before it was released in October 2013.

The Scope of Hematology/Oncology Pharmacy Practice is the first document to clearly define the knowledge, skills, and functions of the hematology/oncology pharmacist, primarily related to direct patient care, and to promote a better understanding of our profession. It also includes a description of the history of oncology pharmacy, the various pathways to specialization in oncology pharmacy, and roles that support the oncology pharmacist.

The uses of the *Scope of Hematology/Oncology Pharmacy Practice* document include not only promoting a better understanding of our profession to consumers, legislators, payers, and other healthcare professionals, but also helping members and HOPA

- define or create job descriptions and responsibilities
- define educational offerings
- define institutional competencies, standards, and certification
- define quality improvement activities
- develop and evaluate pharmacy service delivery systems and organizational structures
- provide roles, challenges, and future directions of profession
- support certification activities
- support health policy advocacy.

The full *Scope of Hematology/Oncology Pharmacy Practice* document can be found on the HOPA website by clicking on the About tab, Press Room, Scope of Hematology/Oncology Pharmacy Practice. Please take some time to review and share with those who you think would benefit from a greater understanding of our profession. 

Save the Date for Celebrating Success: HOPA's 10th Anniversary Gala!

Susannah E. Koontz, PharmD BCOP
Principal and Consultant—Pediatrics
Koontz Oncology Consulting LLC
Houston, TX

To mark the 10th anniversary of our organization, HOPA will be hosting "Celebrating Success: HOPA's 10th Anniversary Gala" during our annual conference in New Orleans on the night of Friday, March 28, 2014. The purpose of the evening is to celebrate our success, recognize key people instrumental in the founding and shaping of HOPA, and raise money to fund future scholastic and research activities of the HOPA Research Foundation Committee. Guests will have the chance to reminisce with one another as we share photos and memories from past conferences and highlight a decade of accomplishment. This is a chance for HOPA to thank its members for their invaluable support over the years.

The celebration will be held at The Chicory, once the largest coffee warehouse in the country, which is just a 5-minute walk from the conference hotel. The evening of fun will include a buffet dinner featuring creole cuisine and an open bar along with live entertainment provided by some of New Orleans' finest jazz musicians. Attire for the event is festive casual.

The Gala Task Force is hard at work planning a memorable evening (and a surprise or two along the way!). Members of the task force include Susannah Koontz (Chair), Dave Baribeault, Courtney Cavalieri,

Liz Hanson, Phil Johnson, Jim Koeller, Bill Petros, Lisa Savage, Jerry Siegel, and Suzanne Simmons (HOPA Executive Director). The group will provide updates on their progress, so be sure to watch for news on HOPA's social media outlets and the Annual Conference webpage.

Don't delay in purchasing your Gala tickets when sales commence at the opening of conference registration, as this will be one event you won't want to miss! At the time of ticket purchases, members will have the opportunity to make a donation toward the HOPA Research Foundation Committee. All donors will receive special recognition during the Gala.

As you make plans to attend the annual conference, please hold the evening of Friday, March 28, to join your colleagues at the Gala. We look forward to seeing you in New Orleans! 



Afatinib (Gilotrif™)

Class: Tyrosine kinase inhibitor

Indication: First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with exon 19 deletions or exon 21 (L858R) substitution epidermal growth factor receptor (EGFR) mutations

Dose: 40 mg orally once daily on an empty stomach

Dose modifications: Hold afatinib for \geq grade 3 National Cancer Institute Common Terminology Criteria for Adverse Events, diarrhea of grade 2 or higher persisting for 2 or more consecutive days, cutaneous reactions of grade 2 that are prolonged or intolerable, or for renal dysfunction of \geq grade 2. Resume treatment at a reduced dose when adverse event fully resolves, returns to baseline, or improves to grade 1. For patients who require therapy with a P-glycoprotein (P-gp) inhibitor, reduce afatinib daily dose by 10 mg if not tolerated. For P-gp inducers, increase afatinib daily dose by 10 mg as tolerated.

Common adverse effects (>30% incidence): Diarrhea, stomatitis, rash/dermatitis, dry skin, and paronychia

Serious adverse effects: Pulmonary toxicity/interstitial lung disease (ILD)-like adverse reactions, sepsis, and pneumonia

Drug Interactions: P-gp inhibitors and inducers

Afatinib for Metastatic Non-Small Cell Lung Cancer

Ashley N. Huddleston, PharmD

PGY2 Hematology/Oncology Pharmacy Resident

The Nebraska Medical Center, University of Nebraska Medical Center College of Pharmacy

Omaha, NE

Lung cancer is the second most common cancer type in both men and women. It has been estimated that 228,190 patients will be diagnosed with lung cancer in 2013. Lung cancer represents approximately 14% of all cancer diagnoses and accounts for more deaths than any other cancer in both men and women. It is estimated that 159,480 deaths will occur secondary to lung cancer in 2013.¹ The World Health Organization (WHO) classifies lung cancer into two major categories based on biology—small-cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC); approximately 95% of all lung cancer patients fall into one of these two diagnoses. Most cases are NSCLC, which comprises approximately 85% of lung cancer diagnoses.¹ The 5-year survival rate (approximately 4%) for metastatic disease is poor.¹

For advanced or metastatic disease, chemotherapy combined with radiation with or without palliative surgery is considered to be the mainstay of treatment for NSCLC. A platinum-based doublet (such as cisplatin/pemetrexed) is recommended for patients with a good performance status, while single agents can be offered to elderly patients and those with a poor performance status. However, metastatic

disease generally carries a poor prognosis with few effective treatment options available. Due to the poor survival rate with metastatic NSCLC, new therapeutic options are being pursued for metastatic disease, such as targeted therapies based on current knowledge of mutations occurring in the NSCLC cells. Available targeted therapies for NSCLC include bevacizumab, which is a recombinant monoclonal antibody against the vascular endothelial growth factor (VEGF); cetuximab, a recombinant monoclonal antibody against epidermal growth factor receptor (EGFR); and tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib, and crizotinib.²

Several biomarkers have been identified that may be objectively measured and utilized as prognostic and predictive factors for NSCLC. EGFR, the 5' endonuclease of the nucleotide excision repair complex (ERCC1), the KRAS oncogene, and the ALK fusion oncogene are likely the most clinically significant with regard to treatment outcomes.² EGFR mutations occur in 10%–30% of NSCLC patients, with higher rates observed in women, patients with adenocarcinoma cancer types, and those who have never smoked.³ Detecting EGFR mutations does not appear to be a prognostic factor; however, the presence of this mutation is predictive of treatment benefit from EGFR-TKI therapy.⁶

Afatinib (Gilotrif, Boehringer Ingelheim Pharmaceuticals, Inc) is an oral TKI that was approved by the U.S. Food and Drug Administration (FDA) on July 12, 2013.⁵ Afatinib is indicated for the first-line treatment of patients with metastatic NSCLC with EGFR exon 19 deletions or exon 21 substitution mutations as detected by the Therascreen® EGFR RGQ PCR Kit, which was FDA approved along with afatinib. Afatinib covalently binds to the kinase domains of EGFR, HER2, and HER4 and irreversibly inhibits tyrosine kinase autophosphorylation, resulting in downstream regulation of the ErbB signaling.⁶ The ErbB intracellular signaling pathway controls key cellular processes including proliferation, cell migration, metabolism, and survival.³ For patients with sensitizing EGFR mutations, the National Comprehensive Cancer Network recommends erlotinib as first-line therapy for patients with EGFR mutations.² Unfortunately, patients can experience disease progression due to acquired resistance mechanisms against oral TKIs such as erlotinib and gefitinib.

Afatinib has demonstrated in vitro inhibition of autophosphorylation of cells expressing wild-type EGFR; therefore, it could be considered for EGFR wild-type NSCLC.² In addition, the pharmacologic activity of afatinib against EGFR-mutated NSCLC was evaluated in a phase 1/2 trial.⁶ In vivo, afatinib inhibited EGFR and HER-2/neu tyrosine phosphorylation and tumor cell proliferation. Importantly, afatinib was active against tumors overexpressing EGFR with the secondary Thr790Met point mutation, which confers resistance to the first-generation EGFR inhibitors gefitinib and erlotinib.⁷ Because it does have activity in cells possessing resistance to these TKIs, it could be considered either first or second line for EGFR-wild-type or mutated NSCLC.^{2,6}

The safety and efficacy of afatinib was evaluated in the LUX-Lung 3 Study. This study was a multicenter, international, open-label, randomized trial enrolling 345 patients with metastatic NSCLC whose tumors

tested positive for EGFR mutations.⁷ Patients were randomized 2:1 to receive afatinib 40 mg orally daily ($n = 230$) or pemetrexed 500 mg/m² and cisplatin 75 mg/m² every 21 days ($n = 115$). The primary efficacy endpoint was progression-free survival (PFS) as assessed by an independent review committee. Secondary endpoints included tumor response, overall survival (OS), adverse events, and patient-reported outcomes (PROs). Treatment continued until investigator-assessed disease progression. Randomization was stratified according to EGFR mutation status and race. A statistically significant prolongation in PFS was demonstrated for patients in the afatinib arm with a median PFS of 11.1 months versus 6.9 months in those receiving traditional chemotherapy (hazard ratio [HR] 0.58; 95% confidence interval [CI]: 0.43–0.78; $p < .001$). Objective response rates were 50.4% and 19.1% in the afatinib and traditional chemotherapy arms, respectively. For patients with exon 19 deletions or exon 21 substitution mutations, the median PFS was 13.6 months versus 6.9 months in the afatinib and traditional chemotherapy arms, respectively (HR 0.47; 95% CI: 0.34–0.65; $p = .001$).⁸ At the time of publishing this trial, OS data were not available; however, the primary analysis for OS is scheduled to occur when approximately 209 deaths are observed.

The most common adverse effects ($\geq 20\%$ of patients) reported in trials with afatinib were diarrhea, stomatitis, rash/dermatitis, pruritus, dry skin, paronychia, and decreased appetite. Diarrhea occurred in 96% of patients treated with afatinib and resulted in renal impairment in 6.1% of cases.⁶ Patients should be provided with an antidiarrheal agent such as loperamide for self-administration at onset of diarrhea and continued until 12 hours after loose bowel movements have ceased. Cutaneous reactions including rash, erythema, and acneiform rash occurred in 90% of patients, and grade 3 reactions occurred in 16% of patients. Serious skin reactions include bullous blistering and exfoliative lesions. Patients should be advised to minimize sun exposure with sunscreen while taking afatinib and to report any new skin lesions because a dose reduction may be necessary. Other serious but rare adverse events reported include interstitial lung disease (ILD), keratitis, sepsis, and left ventricular dysfunction, therefore patients should be advised to report any new or worsening lung problems, vision changes, or swelling of ankles, feet, or legs. Laboratory abnormalities associated with afatinib include increased alkaline phosphatase, hypokalemia, and increased aspartate aminotransferase.⁶

The FDA-approved dose of afatinib is 40 mg orally once daily. Tablets are commercially available in 40 mg, 30 mg, and 20 mg, allowing for ease of dosing and dose modifications. Afatinib should be taken on an empty stomach at least 1 hour prior to or 2 hours after a meal. Treatment should be continued until disease progression or unacceptable toxicity.

Afatinib should be withheld for any adverse event of grade 3 or higher and can be resumed at a reduced dose when adverse reaction fully resolves, returns to baseline, or improves to grade 1. Afatinib also should be withheld for diarrhea of grade 2 or higher persisting for 2 or more consecutive days while taking an antidiarrheal medication. Withhold afatinib for cutaneous skin reactions of grade 2 that are prolonged (persisting more than 7 days) or intolerable, or for renal dysfunction of

grade 2 or higher. For specific information regarding dose reductions, refer to the manufacturer's package insert. Afatinib should be permanently discontinued for any of the following adverse reactions:

- life-threatening bullous, blistering or exfoliative skin lesions
- confirmed ILD
- severe drug-induced hepatic impairment
- persistent ulcerative keratitis
- symptomatic left ventricular dysfunction
- severe or intolerable adverse reaction occurring at a dose of 20 mg per day.

For patients who require therapy with P-gp inhibitors such as cyclosporine, tacrolimus, or ketoconazole, the daily dose of afatinib should be reduced by 10 mg to prevent toxicity of afatinib caused by decreased metabolism. The previous dose can be resumed as tolerated when the P-gp inhibitor is discontinued. For patients requiring chronic therapy with P-gp inducers such as prazosin or rifampin, the daily dose of afatinib should be increased by 10 mg as tolerated. Resume the previous dose 2 to 3 days after the P-gp inducer is discontinued. Afatinib is not an inhibitor or inducer of the cytochrome P450 enzyme system, so drug interactions with concomitant medications that utilize the CYP450 enzyme system are unlikely.

When taken with a high fat meal, C_{max} is decreased by 50% and AUC is decreased by 39% relative to the fasted condition.⁶ Median trough plasma concentrations in patients with mild or moderate renal impairment were 27% and 85% higher than those in patients with normal renal function. However, afatinib has not been extensively studied in patients with severe renal impairment because the drug is eliminated mainly by biliary/fecal excretion. Mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment had no influence on drug exposure following a single dose. Patients with severe (Child Pugh C) hepatic impairment have not been extensively studied; therefore, patients receiving afatinib with hepatic impairment should be monitored closely for toxic effects. The half-life of afatinib is approximately 37 hours.⁶ Afatinib has demonstrated embryofetal toxicity in animal studies and, based on its mechanism of action, could cause fetal harm when administered to a pregnant woman. Therefore, if used during pregnancy or if the woman becomes pregnant while taking afatinib, the patient should be aware of the potential harm to the fetus. In addition, it is unknown whether afatinib is present in human breast milk, therefore a decision should be made on whether to continue afatinib in nursing mothers, taking into account the importance of the drug to the mother.⁶

Patients with metastatic NSCLC have poor long-term outcomes and limited effective treatment options. Afatinib is a newly approved TKI for the treatment of this aggressive disease. The LUX-Lung 3 trial demonstrated a prolongation of PFS for patients with identified exon 19 deletions or exon 21 substitution mutations, as detected by the FDA-approved therascreen[®] mutation test. Afatinib should be considered either first or second line for the treatment of EGFR mutated NSCLC. Overall, afatinib is well-tolerated with the most common adverse events being gastrointestinal and dermatologic in nature.

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The application deadline is January 6, 2014.

More information can be found on the HOPA website, www.hoparx.org.

Denosumab (Xgeva®)

Class: Monoclonal antibody, RANKL inhibitor

Indication: Treatment of adults and skeletally mature adolescents with giant cell tumor of the bone that is unresectable or where surgical resection is likely to result in severe morbidity

Dose: 120 mg every 4 weeks, plus an additional 120-mg dose on day 8 and day 15 of the first month of therapy

Dose modifications: No specific dose adjustments are currently recommended. Use with caution in patients with creatinine clearance less than 30 mL/min due to an increased risk of hypocalcemia.

Common adverse effects: Fatigue, asthenia, back pain, arthralgia, headache, nausea, diarrhea, hypocalcemia, hypophosphatemia, pain in extremity, dyspnea, cough

Serious adverse effects: Osteonecrosis of the jaw, severe hypocalcemia (<7 mg/dL corrected), severe hypophosphatemia (<2 mg/dL), atypical femur fracture, hypersensitivity reactions, embryofetal toxicity

Drug interactions: No clinically significant drug interactions have been reported. Concomitant use with immunosuppressive agents may increase the risk of infection. Use with agents that decrease serum calcium may have an additive effect.

Denosumab for Giant Cell Tumor of Bone

Matthew Arango, PharmD

PGY1 Pharmacy Practice Resident

Cleveland Clinic, Cleveland, OH

Giant cell tumor of the bone (GCTB) is a primary osteolytic tumor that occurs most often in young adults, typically between 20 and 40 years of age.¹⁻³ It comprises approximately 20% of benign bone tumors in the United States.² Although GCTB is typically benign, it is associated with significant pain and decreased range of motion as a result of localized bone and tissue destruction. Pathologic fractures can also occur and may be the initial impetus for presentation to a physician. GCTB lesions may cause neurologic deficits when the site of bone infiltration involves the spine, sacrum, or base of the skull. The metastatic potential of the disease is low, but as many as 6% of patients will develop spread of the primary tumor, most often to the lungs.⁴ In addition, GCTB cells may undergo malignant transformation after radiation therapy or multiple disease recurrences.²

Histologically, GCTB is defined by the presence of large numbers of multinucleated osteoclast-like cells which express the receptor activator of NF- κ B (RANK). Stromal cells within the giant cell tumor express high levels of RANK ligand (RANKL). RANKL has been shown in animal models to be necessary for osteoclast pathophysiology and it is believed that increased RANKL expression is responsible for the recruitment of osteoclast-like cells and tumor growth in GCTB.^{1,2} The

disease has historically been managed with surgical resection or curettage. Recurrence approaches 20% in patients who undergo surgery alone; however, when local adjuvant therapy is used in combination with surgery, recurrence rates are between 8%–17%.¹ Surgical treatment can cause significant morbidity and may not be possible in all cases. Disease located in the sacrum or axial spine increases the risk of surgical complications and radiation therapy is frequently used in such cases. Recurrent disease after radiation therapy is common and radiation may increase the risk of malignant transformation of GCTB. Bisphosphonates, interferon, and traditional chemotherapy have all been used to treat GCTB, although none are U.S. Food and Drug Administration (FDA) approved for this purpose.¹⁻⁴ The data are limited to small retrospective studies and case reports with varied results. The discovery of RANKL overexpression in GCTB and other bone diseases makes it an attractive drug target for the treatment of osteolytic disease.

Denosumab (Xgeva®, Amgen Inc.) is a fully human monoclonal antibody directed against RANKL.⁵ By binding RANKL and preventing interaction with its receptor, denosumab decreases osteoclast formation and activity, which prevents bone resorption, increases bone mass, and ultimately, prevents fracture. Denosumab was initially approved in June 2010 under the trade name Prolia® for the treatment of postmenopausal women with osteoporosis at high risk for fracture. The FDA expanded the approved uses for Prolia® in September 2011 to include an indication for increasing bone mass in patients who are at high risk of fracture from receiving androgen deprivation therapy or adjuvant aromatase inhibitor therapy. The dose for these indications is 60 mg once every 6 months. Denosumab received FDA approval under the trade name Xgeva® in November 2010 for the prevention of skeletal-related events (SREs) in patients with bone metastases from solid tumors. The drug was approved at a dose of 120 mg once every 4 weeks. Most recently, the labeling of Xgeva® was expanded on June 13, 2013, to include treatment of adults and skeletally mature adolescents with GCTB that is unresectable or where surgical resection is likely to result in severe morbidity. The approved dosage for GCTB is 120 mg once every 4 weeks, with additional 120 mg doses on days 8 and 15 during the first month of therapy.^{5,7}

Denosumab was approved for GCTB on the basis of two phase 2 open-label multicenter trials.^{4,6} The first trial, conducted by Thomas and colleagues, enrolled 37 patients with recurrent or unresectable GCTB. The primary efficacy endpoint was the percentage of patients with a tumor response defined as $\geq 90\%$ elimination of giant cells relative to baseline between weeks 5 and 25 of therapy; complete elimination of giant cells when giant cells represented <5% of tumor cells at baseline; or lack of radiologic progression by week 25. Of the 35 patients with available data, 86% met the primary outcome (20 of 20 by histology, 10 of 15 by radiology). In addition, 84% of patients experienced investigator-reported clinical benefit, such as reduced pain and improved functional status. Two patients (5%) discontinued the study prior to completion of planned treatment because of disease progression.⁶

The safety and efficacy of denosumab for treatment of GCTB were further evaluated in an international open-label, parallel-group trial by Chawla and colleagues that enrolled 282 patients, including 10

skeletally mature adolescents, with histologically confirmed and radiologically measurable disease. The primary endpoint was safety, which is discussed below. The major secondary outcome was change in disease status, which was determined by the investigators. Out of 252 evaluable patients who received at least 6 months of therapy, 119 (47%) had either a complete or a partial response and 131 (52%) had stable disease without progression. Objective radiologic tumor response was assessed by retrospective, independent review and was noted for 72% (136 of 190) of patients with available images. The authors also reported that 74 of 100 patients with resectable disease who had a surgery planned before beginning denosumab did not require that surgery. In addition, 16 of the 24 patients who underwent a previously planned surgery required a less morbid procedure than was originally planned.⁴

Adverse effects reported in the two trials evaluating denosumab for use in GCTB were similar to those reported previously.^{4,6,7} Almost 90% of patients reported at least one adverse event; the most commonly reported were (>10% incidence) arthralgia, headache, nausea, fatigue, back pain, and pain in the extremity. Treatment discontinuation due to adverse events was rare, occurring in fewer than 5% of patients. Use of denosumab resulted in an incidence of hypocalcemia of 4.7%, with no cases of severe hypocalcemia. Severe hypophosphatemia occurred in 3.2% of patients. The incidence of osteonecrosis of the jaw (ONJ) was 1%, and it occurred roughly 13–20 months after initiation of denosumab.⁴ No patients in either trial developed a hypersensitivity reaction and no patients were observed to have developed neutralizing antibodies against denosumab.⁶

No specific dose adjustments are recommended for patients with hepatic or renal dysfunction. Patients with a creatinine clearance of less than 30 mL/min are at increased risk for hypocalcemia and should be monitored closely. Denosumab is a pregnancy Category D drug and should not be used in patients who are pregnant. It is not known if denosumab is excreted into human breast milk. Denosumab has not been studied for use in a pediatric population with the exception of skeletally mature adolescents. Patients older than 65 years were well represented in clinical trials, and no significant differences in either safety or efficacy were noted between geriatric patients and younger patients.⁷

To date, no formal drug interaction trials have been conducted with denosumab and no clinically relevant interactions have been reported.⁷ In clinical trials, denosumab was associated with an increased incidence of infection compared to placebo, and therefore there may be a theoretical interaction with immunosuppressive medications, but this has not been reported clinically. Denosumab has not been studied in combination with bisphosphonates and concomitant use could increase the risk of potentially severe adverse effects, such as hypocalcemia and ONJ.⁸

Denosumab for the treatment of GCTB is supplied as Xgeva[®] by Amgen Inc. as a single-use vial containing 120 mg/1.7 mL. It must be kept in a refrigerator between 2°C and 8°C until ready for use. When ready for administration, denosumab should be brought to room temperature by allowing the vial to stand 15–30 minutes. Do not expose

it to direct heat or light. The solution should be clear and colorless to pale yellow, and should be discarded if cloudy. Denosumab is administered as a subcutaneous injection in the upper arm, upper thigh, or abdomen. Once brought to room temperature, unused solution should be discarded within 14 days.⁷

The manufacturer considers denosumab to be contraindicated in patients with a history of significant hypersensitivity to the drug or who are hypocalcemic. Patients should receive calcium and vitamin D supplementation while being treated with denosumab and hypocalcemia should be corrected prior to administration. Patients should be counseled on the signs and symptoms of a potential hypersensitivity reaction or hypocalcemia. Patients should practice proper oral hygiene and should avoid invasive dental procedures while receiving denosumab. In addition, women of child-bearing age should be counseled on the use of effective contraception during treatment and for at least 5 months after treatment with denosumab due to the risk of fetal harm and the long elimination half-life of the drug.⁷

GCTB is an osteolytic tumor that causes significant morbidity and has historically required surgical intervention. Denosumab is a monoclonal antibody directed against RANKL and was recently approved for the treatment of patients with unresectable GCTB or those for whom surgery is likely to result in significant morbidity. Denosumab was well-tolerated in clinical trials and was shown to be efficacious with a low incidence of disease progression and a high incidence of clinical benefit. Current studies have a short duration of follow-up and further results are required to assess the long-term safety of denosumab as well as the optimal duration of treatment.

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Protein-Bound Paclitaxel (Abraxane®)

Class: Microtubule inhibitor

Indication: Adenocarcinoma of the pancreas

Dose: 125 mg/m² intravenously over 30–40 minutes on days 1, 8, and 15 of each 28-day cycle; administer gemcitabine immediately following each protein-bound paclitaxel dose.

Dose modifications: Protein-bound paclitaxel should not be administered to patients with moderate to severe hepatic impairment, and the dose should be reduced or held for neutropenia or thrombocytopenia. The dose should be dose adjusted for patients experiencing grade 3 or 4 febrile neutropenia, peripheral neuropathy, and gastrointestinal toxicity, and for patients experiencing grade 2 or 3 cutaneous toxicity.

Common adverse effects: Neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, dehydration

Serious adverse effects: Abraxane® holds a black box warning for neutropenia. Serious side effects include sepsis, pneumonitis, pyrexia, vomiting, and dehydration.

Drug interactions: Inducers and inhibitors of CYP2C8 and CYP3A4 should be administered with caution in conjunction with protein-bound paclitaxel.

Protein-Bound Paclitaxel for the Treatment of Adenocarcinoma of the Pancreas

Devon M. Greer, PharmD

PGY2 Hematology/Oncology Pharmacy Resident

The Nebraska Medical Center/University of Nebraska Medical Center College of Pharmacy

Omaha, NE

In 2013 an estimated 45,220 patients will be diagnosed with pancreatic cancer in the United States and approximately 38,500 patients will die from their disease.¹ Pancreatic adenocarcinoma ranks as the fourth most common cause of cancer-related death in both men and women in the United States, and the diagnosis is often associated with a poor prognosis.¹ Surgical resection is the only means of potential cure for the disease; however, more than 80% of patients diagnosed with the disease will not have this option.² For patients with metastatic or unresectable disease, the goal of therapy is palliation and improved survival.² Gemcitabine therapy has been shown to provide survival benefits in patients with advanced or metastatic disease as monotherapy; however, combinations with this medication have historically provided only marginal improvements in overall survival while significantly increasing the toxicity of the regimen.^{3,4}

Abraxane® is an albumin-bound injectable suspension of paclitaxel that was approved by the U.S. Food and Drug Administration (FDA) on September 6, 2013, for first-line therapy of metastatic

adenocarcinoma of the pancreas, in combination with gemcitabine.⁵ Protein-bound paclitaxel induces the assembly and stabilization of microtubules, thereby interrupting the cell cycle.⁶ Pancreatic ductal adenocarcinoma has been associated with an increase in the expression of secreted protein acidic and rich in cysteine (SPARC), also known as osteonectin.⁷ This albumin-bound protein has been found to be overexpressed in a variety of cancers, including breast, lung, and melanoma.⁸⁻¹⁰ Protein-bound paclitaxel has been shown to provide antitumor effects in each of these tumors and currently holds an FDA indication for the treatment of metastatic breast cancer and non-small cell lung cancer.⁶ The use of albumin-bound paclitaxel may work synergistically in combination with cytotoxic agents by targeting SPARC within the stroma and assisting in the effective delivery of gemcitabine to the tumor.⁷ This allows for improved pharmacokinetics over cremophor-paclitaxel.¹¹

In a phase 1/2 study, protein-bound paclitaxel, in combination with gemcitabine, was found to have substantial antitumor activity in patients with advanced metastatic pancreatic adenocarcinoma.¹¹ Patients receiving protein-bound paclitaxel at 125 mg/m² and gemcitabine 1,000 mg/m² had a response rate of 48% and a median overall survival (OS) of 12.2 months.¹¹ The combination of the two agents had tolerable adverse effects, with the most frequent dose-limiting toxicities being sepsis and neutropenia.¹¹

The FDA approval of Abraxane® for metastatic pancreatic adenocarcinoma was based on the data from a phase 3, multicenter, international, open-label, randomized trial in which protein-bound paclitaxel with gemcitabine was compared to gemcitabine monotherapy as first-line treatment in 861 patients with metastatic adenocarcinoma of the pancreas.⁶ Patients were randomized in a 1:1 manner to receive either gemcitabine monotherapy or gemcitabine plus protein-bound paclitaxel. Stratification of patients was then performed on the basis of geographic location, performance status, and the presence of liver metastasis.⁶ The primary endpoint in the study was OS with secondary outcomes of progression-free survival (PFS) and overall response rate (ORR). Both secondary endpoints were evaluated by an independent, central, blinded radiographic reviewer.⁶

Patients in the intent to treat population had a median age of 63 years (range 27–88 years); however, 42% of patients randomized were older than 65 years of age. The majority of patients were male (58%), and the Karnofsky performance status (KPS) was at least 90 in 60% of the patients. Almost half of the patients randomized had three or more metastatic sites (46%), with the vast majority having liver metastasis (84%).⁶ Disease characteristics included the primary pancreatic lesion located in the head, body and tail of the pancreas in 43%, 31%, and 25% of patients, respectively.⁶

The gemcitabine monotherapy group ($n = 430$) received gemcitabine at 1,000 mg/m² as an intravenous (IV) infusion over 30–40 minutes once a week for a total of 7 weeks, followed by a 1-week resting period for the first cycle.⁶ Patients were then administered gemcitabine 1,000 mg/m² on days 1, 8, and 15 of each following 28-day cycle. Patients randomized to the combination group ($n = 431$) received

protein-bound paclitaxel 125 mg/m² as an IV infusion over 30–40 minutes immediately followed by gemcitabine 1,000 mg/m² IV over 30–40 minutes on days 1, 8, and 15 of each 28-day cycle. Patients were treated until disease progression or until toxicity occurred requiring drug discontinuation; cross-over was not permitted.⁶

The trial illustrated that OS was significantly prolonged in patients receiving the combination therapy of gemcitabine and protein-bound paclitaxel versus gemcitabine monotherapy (hazard ratio [HR] 0.72 [95% confidence interval [CI]: 0.62, 0.83]; $p < .0001$), with a median OS of 8.5 months in the combination group compared to 6.7 months in the monotherapy group.⁶ For the secondary outcomes, the addition of Abraxane[®] to gemcitabine improved PFS compared with monotherapy (5.5 months versus 3.7 month, HR 0.69 [95% CI: 0.58, 0.82]; $p < .0001$) and provided greater rates of response. The rate of confirmed complete or partial responses in the combination group was 23% ($n = 99$) versus 7% ($n = 31$) in the monotherapy group ($p < .0001$).⁶

Adverse events most frequently reported ($\geq 20\%$ of patients) with Abraxane[®] in combination with gemcitabine included neutropenia, thrombocytopenia, fatigue, peripheral neuropathy, nausea, vomiting, diarrhea, alopecia, peripheral edema, pyrexia, rash, decreased appetite, and dehydration.⁶ Grade 3–4 toxicities occurred more frequently in the combination group versus the monotherapy group. Patients in the combination group received a longer median treatment duration of 3.9 months compared with 2.8 months in the gemcitabine monotherapy group.⁶ In postmarketing surveillance, protein-bound paclitaxel was found to cause severe and sometimes fatal hypersensitivity reactions. Reports of pulmonary embolism and pneumonitis, especially in patients receiving concurrent radiation therapy, have been noted. In addition, visual changes secondary to cystoid macular edema have been reported.

The FDA-approved dose of Abraxane[®] is 125 mg/m²; however, manufacturer recommendations include dose adjustments in the setting of thrombocytopenia, neutropenia, febrile neutropenia (grade 3–4), peripheral neuropathy (grade 3–4), cutaneous toxicity (grade 3–4), or grade 3 mucositis or diarrhea.⁶ Dose adjustments range from decreasing the dose of protein-bound paclitaxel from 125 mg/m² to 100 mg/m² and gemcitabine from 1,000 mg/m² to 800 mg/m² to withholding doses or discontinuing therapy if multiple dose adjustments are necessary.⁶ Dose reduction recommendations are available in the package insert for patients experiencing any of the above toxicities. Abraxane[®] currently holds a black box warning for neutropenia and should not be administered to patients with a baseline neutrophil count of less than 1,500 cells/mm³. Routine monitoring of the patient's peripheral blood counts is recommended during therapy.⁶ In addition, Abraxane[®] is extensively hepatically metabolized by CYP2C8 and CYP3A4 and therefore is not recommended for patients with moderate to severe hepatic impairment.⁶

Due to the role of CYP2C8 and CYP3A4 in the metabolism of protein-bound paclitaxel, Abraxane[®] should not be concomitantly administered with medications known to induce or inhibit these enzymes, including particular imidazole antifungals and antiretrovirals,

carbamazepine, and phenytoin.⁶ Protein-bound paclitaxel is excreted through nonrenal mechanisms, with only 4% excreted as unchanged drug in the urine.² The half-life is predicted to be approximately 27 hours.⁶

Abraxane[®] is a pregnancy Category D drug.⁶ It has not been studied for safety in pregnant women, but animal studies have suggested fetal harm when administered to rats during pregnancy. It is not known if protein-bound paclitaxel is excreted in human breast milk.⁶ The safety and efficacy of protein-bound paclitaxel has not been studied in pediatric patients.⁶ No dosage adjustments are required for geriatric patients; however, diarrhea, decreased appetite, dehydration, and epistaxis occurred more frequently in patients >65 years of age.⁶

Abraxane[®] is available in a 100-mg single-use vial. Once reconstituted, each mL contains 5 mg of protein-bound paclitaxel.⁶ The suspension, once reconstituted, should be milky in appearance and free of particulate matter. The use of specialized DEHP-free containers is not required and the use of an in-line filter is not recommended.⁶

Patients with metastatic pancreatic adenocarcinoma have poor long-term outcomes and limited effective therapy options. Abraxane[®], in combination with gemcitabine, has shown to improve OS, PFS, and ORR, with a tolerable increase in the regimen's toxicity.^{6,11}

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