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Hematology/Oncology Pharmacy Association Newsletter Winter 2010

HOPA News

## Pharmacist CE Credit at the ASH Annual Meeting: Survey Results

*Prepared by: R. Donald Harvey, PharmD, FCCP, BCPS, BCOP*

**BACKGROUND:** In September 2009, a survey from the Professional Affairs Committee went out to the HOPA membership asking for feedback on the need and utility for continuing education (CE) credit for pharmacists at the American Society of Hematology (ASH) annual meeting. The topic was developed for a member survey following the institution of ACPE-approved continuing education credit at the American Society of Clinical Oncology (ASCO) and discussions with ASH organizational staff.

The purpose of the survey was to gauge member interest in claiming CE at the ASH meeting in order to lobby ASH to implement ACPE-accredited programming for pharmacist attendees. Patti Halterman from Professional Affairs developed the survey with review and feedback by committee members, and worked with Meredith Moorman, Katherine McGrath, Stephanie Sutphin, Karen Smethers, and Jane Pruemer from the Survey subgroup of the Membership Committee and Don Fallon from DesignWrite to review, edit, and send to members. Survey questions addressed the priority of the ASH annual meeting to members, overall CE requests, cost concerns, and standard demographic data.

**RESULTS:** Overall, 260 responses were received, for a return rate of 19%. The majority of respondents were full members (91%); worked in either outpatient infusion centers (34%), inpatient settings (44%), and/or were academically affiliated (36%); had been in practice over 15 years (37%); and identified hematology (76.3%) and/or BMT (37%) as a specialty or interest area.

Most respondents only attended one or two national meetings per year (53% and 28%, respectively), 72% always request CE at those meetings, and 86% receive $2000 or less for an annual travel allowance (29% receive no allowance). Interestingly, the lack of availability of a travel allowance was not cited as a restriction for not attending ASH meetings (73%); however, the timing of the ASH annual meeting (being close to the ASHP annual meeting) was a problem for 59%.

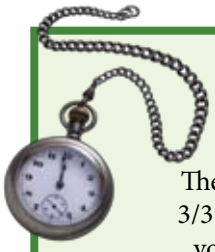
For ASH-specific queries, 90% were not ASH members, 65% had never attended the ASH annual meeting or highlights, and 84% did not plan to attend the 2009 ASH annual meeting. However, if CE were offered at the ASH annual meeting, 78% said they would be more likely to attend.

**CONCLUSIONS:** Following the results of this survey, both ASCO and the American Society of Clinical Pharmacology and Therapeutics (ASCPT) removed ACPE-approved CE from their annual meetings, beginning in 2010. Reasons cited by both groups included the new ACPE requirement for active learning that would increase staff and presenter responsibilities substantially and restrictions on CE for sessions given by industry representatives.

From our survey, it is clear that the majority of respondents see the ASHP meeting as a barrier to attending the ASH meeting. With the changes in ACPE accreditation in mind, as well as the results of our survey, the Professional Affairs Committee has decided to table lobbying ASH for pharmacist CE for the foreseeable future. We thank all members who responded, and all who worked to prepare, review, and summarize results of the survey.

## TABLE OF CONTENTS





### Time to Renew Your HOPA Membership

The membership year expires on 3/31/10. If you have not renewed your membership, please take a moment to renew at www.hoparx.org/Membership.aspx.

# Thank You from the HOPA Board

The HOPA Executive Board would like to thank all of the HOPA committee and task force members who volunteered their time unselfishly over the past year. Without their hard work and dedication, HOPA would not be the strong organization it is today.

The HOPA Executive Board would also like to thank all of the DesignWrite employees who have worked hard with HOPA committees and the Board throughout the year and at the annual meeting, and students from Xavier University of Louisiana College of Pharmacy, who have volunteered their time to help with annual meeting activities.

*Sincerely, the HOPA Executive Board: Phil Johnson, Rowena Schwartz, Cindy O'Bryant, Pat Medina, Mike Vozniak, Jane Pruemer, and Laura Michaud*

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# Risk Evaluations and Mitigation Strategies (REMS): Survey Results

*Prepared by: Scott Soefje, PharmD, BCOP*

In mid-November 2009, the Legislative Affairs Committee surveyed the HOPA membership about their opinions on the Risk Evaluations and Mitigation Strategies (REMS) programs that are now mandated by the FDA for certain new (and in some cases older) medications. This survey was developed out of a concern over the impact these programs are having, or could potentially have, on the pharmacy operations in cancer centers. Reports suggest that there may be as many as 18 to 20 drugs with mandated REMS programs in the near future. With the FDA currently evaluating the need for REMS for opioids, the Legislative Affairs Committee felt this was an appropriate time to survey the membership.

One hundred and fifty-two members filled out at least a portion of the survey. Over 90% were HOPA full members, and the remaining were residents and a few associate members. The majority of responders were practicing at outpatient infusion centers or inpatient hospitals. One-third worked in an institution with an academic affiliation. Nearly 60% of respondents stated that their practice was entirely devoted to hematology/oncology patients.

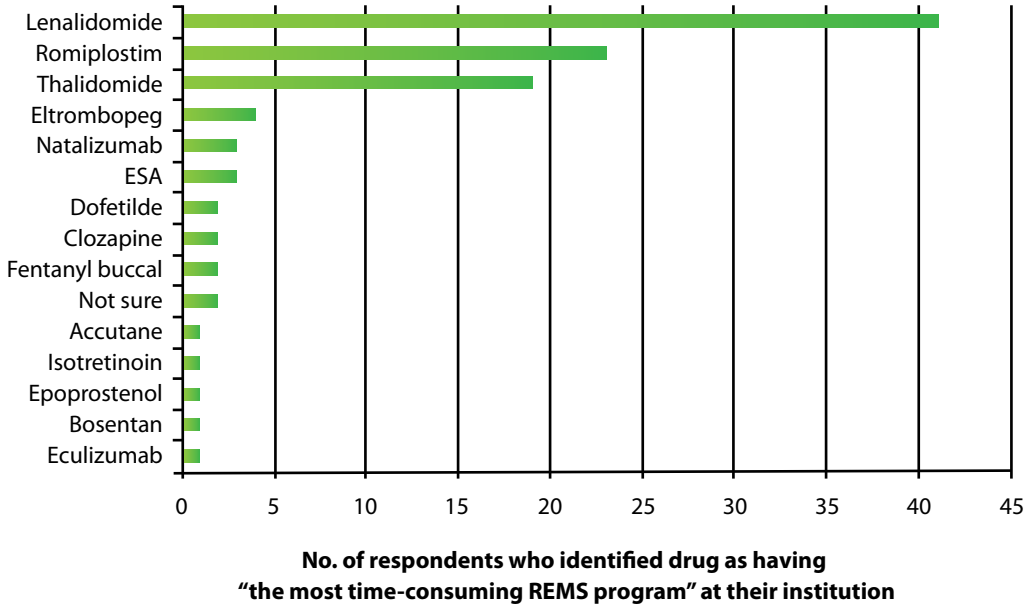
Approximately 75% of the respondents felt that physicians and pharmacists should share responsibility for the required REMS monitoring. Mid-level providers (PAs, nurse practitioners) was the next most common response. When asked who is responsible in their institutions, pharmacists were listed almost 80% of the time. Nurses and prescribers were the next most common response at 33% and 36%. When asked which organization should be responsible for education and certification on REMS programs, the FDA was the overall most common answer at just over 70%. The next most common responses were state boards of pharmacy, national pharmacy organizations, and industry, all at about 30%.

The FDA requires that a single, shared system be used to provide REMS and that the system should have elements to ensure safe use. The FDA has issued guidance for industry regarding REMS programs stating that the proposed programs will minimize the burden on healthcare delivery systems. When asked what obstacles need to be overcome before such a system can exist, the most common response was the need for standardization of the REMS process. Ease of use, time/workload increase, privacy, and reimbursement for services were also mentioned.

Members believe that pharmacists seem to play a variety of roles when dealing with REMS programs. When asked what role the pharmacy should play in REMS programs, the most common responses included education of both providers and patients, but enrollment of patients and documentation for audits and reports were closely behind. About a quarter of the members responding felt that pharmacy should not be involved in REMS programs.

When asked if their pharmacies were involved in REMS programs, 60% stated they were directly involved. Seventy-six percent stated that the pharmacist was responsible for making sure that patient and provider were enrolled in the REMS program when a prescription was received for a drug that required this type of program. When a patient is transferring from one treatment site to another, there was no clear recommendation as to who should be responsible for making sure the new site is ready to accept the REMS patient. Almost 40% of respondents did not know who is responsible, while case manager and pharmacist were the next most common responses. When asked, only one respondent reported that a pharmacist has been reimbursed for medication therapy management services of a REMS program.

**Figure.** Time-Consuming REMS Programs



## REMS (CONTINUED)

Most believed that 10%-20% additional time was required to process the REMS program. However, almost one-third of responses believed that more than 20% additional time was required. Of the agents that require REMS, lenalidomide was cited as the most time-consuming the most often. Other agents mentioned prominently included romiplostim, thalidomide, eltrombopag, and natalizumab (**Figure**). About 40% of pharmacists have been involved in process development for a REMS program. Overwhelmingly, members have not had a report (67%) or did not know of a report (27%) of any outcomes data or preventable event reported by either the FDA or the manufacturer as a result of using the REMS program.

Finally, when asked about opioid REMS, almost 80% of responders were against a REMS program for short-acting opioid medications and 70% were against a REMS program for long-acting opioids. When asked if a program were developed, what elements seen in existing programs should be included, the most common answers were registration of providers, pharmacies, and patients. Only 28% felt pharmacist registration should be included. Over 80% felt patient education or a medication guide should be included and that provider or pharmacist education was important. Two-thirds felt that limiting distribution should not be included.

The REMS programs have the potential to add time and cost to the dispensing of medications. If the projected 18 to 20 drugs have REMS in the future, and considering that in oncology practice, many agents fit the criteria for REMS programs, the impact of these programs could dramatically increase. Our membership generally felt that these programs add time to the dispensing process and that the lack of a standard process and the costs of managing these programs may be a barrier.

It does not seem to be clear to our members the exact role pharmacy should play in these programs. While all agents with a REMS program commonly used in oncology practices received at least one mention as having a time consuming-program, lenalidomide and romiplostim were by far the most commonly mentioned, followed closely by thalidomide (see **Figure**). Our membership did not feel that a REMS program was warranted for opioid medications, but if programs were started then education and registration were the most common elements the members felt should be included. Limited distribution was not recommended.

This survey has generated considerable interest outside of the HOPA membership. The Legislative Affairs Committee has been contacted by several organizations and pharmaceutical companies regarding the results of this survey. This survey has presented an opportunity to partner with other groups that have similar interests, and as a result it will be given to the members of the Association of Community Cancer Centers (ACCC). We intend to pool these results and present a final report to the HOPA membership to provide a broad overview of the impact of REMS programs on oncology practice.

# Preventing Cancer Chemotherapy Errors – Past, Present, and Future Implications

*Ray Muller, MS, RPh, FASHP*
*Memorial Sloan-Kettering Cancer Center*

The headline of the April 14, 1992 edition of the *New York Post* screamed "Rx FOR DEATH" in bold red letters. The article described an incident in which an ovarian cancer patient received CISplatin instead of CARBOplatin (at a dose appropriate for CARBOplatin) and tragically died as a result of the massive overdose. Another incident at one of the world's premier cancer centers in 1994 was a watershed event in oncology practice. Betsy Lehman, a 39-year-old healthcare reporter for one of the country's leading newspapers, died of a cyclophosphamide overdose during treatment for metastatic breast cancer. This single tragic incident forced most academic medical systems to critically evaluate their ordering, dispensing, and administration practices and acted as a tipping point to enhance our ability to prevent cancer chemotherapy errors.

Medication errors and their prevention have always been major concerns for healthcare professionals. The problem prevails as we continue to read highly publicized reports of catastrophic events that are comprehensively summarized in an educational format in the "Medication Safety Alert" that is electronically distributed to thousands of hospitals every 2 weeks by the Institute for Safe Medication Practices (ISMP). Four groundbreaking reports released by the Institute of Medicine are generally recognized as the impetus that launched the modern patient safety movement: "To Error is Human: Building a Safer Health System (2000)"; "Crossing the Quality Chasm: A New Health System for the 21st century (2001)"; "Patient Safety: Achieving a New Standard for Care (2004)"; and "Preventing Medication Errors" (2006). I use this direct quote from the 2000 report: "More patients die every year from medical errors than from automobile accidents, breast cancer, or AIDS"— a statistic that still surprises many attendees at my medication safety lectures. Organizations such as ISMP, National Quality Forum, Agency for Healthcare Research and Quality, World Health Organization, Institute for Healthcare Improvement and others have been very vocal proponents to set national benchmarks and enhance the Joint Commission standards. Components that are universally endorsed by these organizations include: reporting and learning from errors and highlighting the advantages of electronic order entry with appropriate interface technology and with dispensing and administration safeguards. There is also universal agreement that health-system leadership must be more engaged in robust interventions that improve care, such as conducting interdisciplinary root-cause analyses.

Several noteworthy articles have been published recently that are pertinent to HOPA members. I don't have space to dissect each paper but I encourage you to review them. Walsh and colleagues[1] reviewed records from 1262 adult cancer patient visits and 117 pediatric visits and reported that 7% of adult and 19% of pediatric visits were associated with a medication error. Interestingly, and contrary to most general medication studies, errors most commonly occurred in the administration (56%) phase of the medication management process. Administration errors were due to confusion over two sets of orders; one written at diagnosis and another adjusted dose on the day of drug administration. This study is important because it highlights that medication errors among outpatients with cancer is common. The authors review strategies to prevent these errors, including computerized prescriber order entry, electronic medication administration records, and "smart" infusion pumps with limits for high-alert meds including chemotherapy. Among children, more than 50% of the potentially harmful errors were associated with home medication use. The authors advocate improving communication between healthcare providers and the families as a critical step to prevent errors.

ASCO and ONS recently released a joint chemo administration standard[2] that serves as an excellent practice benchmark and includes a set of 31 standards encompassing 7 domains: review of clinical information and selection of treatment regimens; treatment planning and informed consent; ordering of treatment; drug preparation; assessment of treatment compliance; administration and monitoring; and assessment of response and toxicity monitoring. Although several pharmacists

had some input into this standard, it was very disappointing that there was no pharmacist coauthor on this landmark paper. Additionally, neither ASHP or HOPA were apparently invited to formally participate in the development of these standards, even though seminal papers on this topic were published in *AJHP* in 1996 and 2002 by several pharmacists practicing in large cancer centers.[3,4]

In August 2009, we learned of a chemo error that caused the tragic death of a 2-year-old child, Emily Jerry, when a pharmacist failed to recognize that a technician he was supervising used 23.4% sodium chloride, rather than 0.9% normal saline, to prepare an etoposide infusion. Sadly, the pharmacist was sentenced to a 6-month jail sentence and permanent revocation of his pharmacy license (http://www.ismp.org/Newsletters/acutecare/articles/20090827.asp). I share Mike Cohen's sincere conviction that this tragic incident may be precedent-setting for our profession and may drive the open reporting of errors and near-misses underground. Ironically, this will mean that we will miss valuable opportunities to learn from mistakes and improve our systems. It is also another reason why tort reform is needed to change the judicial system from being punitive to being a process for improvement.

I frequently receive phone calls from colleagues asking for advice on how to avoid tragic chemo errors. It's virtually impossible to give cogent information in a "phone consult," as it takes considerable effort to understand unique practice settings and systems. I am usually impressed by the sincere dedication that callers have but also very wary of the "quick fix" mentality that might be conveyed.

My view is that developing systems to prevent chemo errors in our complicated health system represents a long journey that is extraordinarily labor-intensive and requires the very active participation of the oncologist, pharmacist, nurse, and patient or family member. The active participation of the medical informatics team is also integral to this process. In our transition from preprinted order forms at MSKCC, we now have over 2000 order sets in our electronic prescriber order entry program. I believe pharmacists have to be at the leading edge of preventing cancer chemotherapy errors and must be the proactive authority in developing the systems and standards so that our patients have the safest chemotherapy care possible. This includes developing electronic systems with clinical decision support tools (eg, serum creatinine is displayed when carboplatin is ordered); treatment guidelines that are readily available to all practitioners with drug names, allowable doses, schedules, and supportive meds that are standardized; and order sets including dose/route contraindications and maximum allowable doses of chemo agents that can be infused by "smart" infusion pumps. Ideally our systems must have a 100% electronic record so inpatient and ambulatory doses can be displayed. Education and training for all staff members should include knowledge credentialing using case studies for all clinicians that include an open discussion of actual errors and near-misses that have occurred at the center. There should be an electronic "potential error" reporting system that the pharmacist manages that can track and trend concerns with specific drugs or practice areas, reports adverse drug reactions, and that is designed to suggest systematic changes in drug policies or monitoring guidelines. When an actual error does occur, it should be immediately disclosed to the patient with a sincere apology to the patient or family member. The error should be reviewed by a multidisciplinary group including the practitioners involved in the error, and discussed in an open way so all parties can learn to prevent a future recurrence.

Another recently published paper warrants your consideration. Robert Wachter, a physician and nationally recognized patient safety authority published a paper[5] giving a report card grade on nine components of key patient safety domains such as health information technology issues, research, and provider leadership engagement. Dr. Wachter assigned individual component grades from A- to C+, with an overall grade of B-. This largely reflects my sentiments. My cautious optimism, which was reflected 10 years ago upon the release of the first Institute of Medicine report, was that we would have systems in place to prevent all common chemo errors. While we have made very considerable strides in standardizing our systems, reporting, and practices, I think healthcare providers still have quite a distance to travel to create the safest chemo experience possible for our patients—and to achieve the ultimate safe process we also need the full, fair, and objective collaboration of all stakeholders, including the informatics and automation industry, payers, regulatory agencies, and the judicial system.

## Acknowledgement

The author gratefully acknowledges the review of Phil Johnson.

## References

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### R. Donald Harvey Wins HOPA 2010 Research Award

The HOPA Research Committee is pleased to announce that the 2010 HOPA Research Grant was awarded to R. Donald Harvey III of Emory University. The title of his research proposal is "Lenalidomide Pharmacokinetics in Patients with Multiple Myeloma: Effect of Renal Function and Dose Modification on Exposure and Toxicity." Dr. Harvey will be able to begin the research immediately, but will be formally recognized for his award at HOPA 2010 in March.

—HOPA Research Committee

# COMMITTEE UPDATES

## Update from the Board

*Laura Michaud*
*At-Large Board Member*

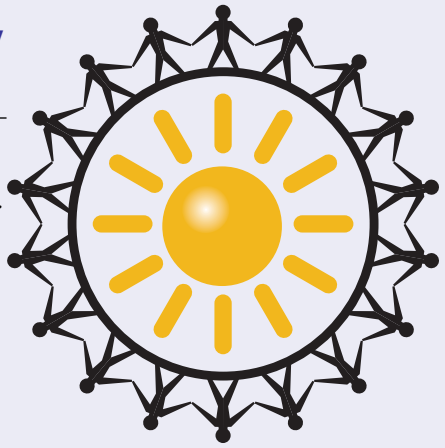
On behalf of the Executive Board, I wish you all a Happy New Year! The Board is excited to report that we are fast approaching our next annual conference, and with the shortened year we seem to be in overdrive! We hope that all HOPA members are able to attend HOPA's 6th Annual Conference, to be held at the New Orleans Marriott, March 24-27, 2010. As a reminder you can go to www.hoparx.org/Hopa2010.aspx to access all needed information about this year's conference.

One focus for the Board over the past year was to improve communications and collaborations between committees, seeking input from all members when possible and expanding the educational offerings we (as an organization) are able to provide. These efforts are seen in the 6th Annual Conference schedule now posted on our website at the link above. All HOPA committees have done an excellent job working together to develop an outstanding, diversified educational program with something for everyone.

Some unique events being offered before, during, and after the annual conference are:

1) **Keynote Address:** We will launch the conference on Wednesday, March 24 with a timely and critical discussion on Healthcare Reform from our distinguished keynote speaker, Dr. Joseph Bailes. Dr. Bailes is a medical oncologist from Houston, formerly the Executive Vice President and CEO of the American Society of Clinical Oncology (ASCO), and has had substantial experience in legislation, public policy, and advocacy. We look forward to Dr. Bailes' informative message and hope to continue to build upon important relationships with organizations such as ASCO.
2) **Oncology Boot Camp:** A new Oncology Boot Camp will be offered prior to the meeting on Wednesday morning. This continuing education program is intended to target educating new practitioners, old practitioners new to oncology, and/or healthcare providers with less than full-time oncology commitment. This is our first year offering this event and we are excited to provide this level of education as an outreach to the New Orleans and southern Louisiana area pharmacists as well as others attending the meeting. See the Education Committee update for more details.
3) **BCOP Item Writer's Workshop:** Calling all BCOPs! The Board of Pharmaceutical Specialties (BPS) is always looking for a few good item writers! They will be holding an Item Writers Workshop to review, build, and maintain the bank of questions used for the specialty examination. This will take place prior to the meeting on Tuesday afternoon, March 23, and Wednesday morning, March 24. Look for e-mails from BPS for more details.
4) **Fun Run/Walk:** Our fundraising event this year will be "Rays of Hope" 5K Run/3K Walk and Membership Charity Drive held in conjunction with our annual conference on Saturday, March 27, 2010 from 6:30 - 8:00 am. Proceeds from this event will benefit Camp Challenge, a local camp for kids fighting cancer. Sign-ups and donations are at www.hoparx.org/2010RunWalk.aspx.
5) **Committee Meetings:** Committee meetings for the current committee members and leadership are planned to be held immediately following the primary programming on Saturday, March 27. Also, the committee selection process is currently underway. If you haven't already responded to the Committee Interest Survey, it will remain open on the members-only section of the website (bottom of page). A link to the survey is at https://www.hoparx.org/membersonly.aspx. You will be asked to log in.

## 2010 HOPA Run/Walk Charity Event: RAYS OF HOPE



*Heather D. Cox, PharmD*
*Oncology Pharmacist*
*Wake Forest University Baptist Medical Center*
*Winston-Salem, NC*

HOPA will host its second annual Run/Walk during the 2010 Annual Meeting in New Orleans. It will be held at Woldenburg Park on March 27th at 6:30 am. HOPA has selected Camp Challenge as this year's recipient of the proceeds. Camp Challenge is a local, non-profit organization in New Orleans that gives oncology/hematology patients from Louisiana, survivors, and their siblings (ages 5-18) a fun and exciting way to spend a week of their summer break at no charge to the families. This year is the 22nd year the camp has been held and it runs completely off the generosity of others. The camp is aimed at giving these children a traditional camp experience that is fun and empowering in a medically safe environment.

Please feel free to attend the race and show your support even if you are unable to participate. To sign up for the 2010 Rays of Hope event and/or to make donations please visit www.hoparx.org/2010RunWalk.aspx. For more information pertaining to Camp Challenge, please visit www.campchallenge.org.

# COMMITTEE UPDATES (CONTINUED)

6) **Virtual Meeting:** There are plans underway to be able to provide much of the annual conference (audio/slides, posters, possibly others) on our website after the meeting. Look for more information on these efforts in the months to come!

Other items the Board has been working on include reviewing and selecting a management company since our contract with our current management company is expiring. We have also tasked a Research and Education Foundation Advisory Council to begin the process of building our foundation. The Council is currently developing by-laws and other documents in order to file for incorporation and begin receiving grant funds. The creation of a foundation will allow us to seek other sources of funding to be used toward more extensive educational and research grants. We developed a Committee Handbook to help guide committee leadership on the functions of their respective committees and the overall operation and inter-relationship between committees and the Board. In addition, we are working on streamlining, consolidating, and standardizing many operating policies and procedures for the organization, task forces, committees, and the Board. We hope that this process will help improve the hand-off process from year to year and encourage collaboration between groups to enhance the entire organization.

All of the committees have worked especially hard this year and have accomplished a great deal. Please read on to see what each of them has been up to lately!

Lastly, the venue for the HOPA 7th Annual Conference has been chosen. We will be congregating in Salt Lake City, Utah from March 23-26, 2011!! We are excited to go to a city we have yet to visit and we hope to see everyone there in March 2011!


## BCOP Recertification Committee

*Amy Hatfield Seung, Chair*
*Julie Burzynski, Vice-Chair*

The BCOP Recertification Committee has reviewed the 6 presentations for the live recertification hours to be provided at the 2010 HOPA Annual Meeting, the ACCP Annual Meeting, and the ASHP Midyear Meeting. The topics include Radiation Oncology, Pediatric Malignancies, Cervical Cancer, Melanoma, Pancreatic Cancer, and the Impact of Technology on Chemotherapy/Anticancer Medication Safety. We are currently developing and validating the BCOP recertification assessment questions using the HOPA standard operating procedures. The committee is collating feedback from the 2009 live sessions to enact changes in future programming. The committee continues to work with ACCP and ASHP to improve the process for individuals seeking BCOP recertification credit at the meetings.

## CE Accreditation Committee

*LeAnne Kennedy, Chair*
*Janet Espirito, Vice-Chair*

**Continuing Changes with Continuing Pharmacy Education:** In the last HOPA newsletter there was an article about ASCO not offering ACPE continuing pharmacy education (CPE) at their 2010 meeting. The reason for this and other organizations not offering ACPE CPE is that it has become harder to document the active learning process that is now required for ACPE-approved CPE. For every activity, ACPE requires that there is a planned needs assessment, active learning objectives defined, and measurement of these objectives during the activity. This is a very laborious and intensive process (one to which HOPA is committed), but for multidisciplinary organizations such as ASCO and ASCPT it is more than they are willing and able to commit to, especially when pharmacists are not the primary audience for their programming. For clarification, the standards that ACPE has adopted also apply to physicians, nurses, and other healthcare professionals. However, pharmacy is really leading the way for continuing education and we hope that HOPA is setting an example for pharmacy continuing education.

You will continue to see some more changes at our annual meeting this year. Audience response system (ARS) will be used again to help engage you, the audience, in active learning. There may be times (especially in the workshops) where you will be asked to participate in group discussions. This way we will be able to share information back and forth. We will continue to use self-assessment questions to measure learning, and these questions will be provided to attendees beforehand, in a printable format, online at HOPA U. That way you may take

### HOPA Awarded ACPE Accreditation Through 2013

We are excited to announce that the Accreditation Council for Pharmacy Education (ACPE) has accredited HOPA as a provider of continuing pharmacy education through 2013. Part of the reason that we no longer need yearly review by ACPE is that we have worked hard to find ways to engage our learners and make their participation in HOPA-sponsored CPE activities as active as possible. You have seen many of these changes at the HOPA annual meetings over the last 2 years, and at this year's meeting you will be asked to participate even more. Our goal is to help you both retain what you learn and take it back home to use in your day-to-day care of hematology and oncology patients. We want to make sure that each and every participant in HOPA-sponsored CPE activities gets the most out of the programming they attend, at our annual meeting, and at HOPA's educational website www.hopaU.org.

# COMMITTEE UPDATES (CONTINUED)

notes for when you go online to complete your meeting evaluation in order to obtain your CPE credit.

## Education Committee

*Sarah Scarpace, Chair*
*Susannah Koontz, Vice-Chair*

With just a short time until our annual meeting, the Education Committee continues to make great progress on several projects and initiatives. We are in the process of presenting our committee's two standard operating procedures (SOP) to the Board for their review and approval. This comes just weeks after the SOPs were drafted by a few of our members (Best Practices – Katie Tipton, Laura Wiggins, Robert Morris, and Brandy Strickland; Patient Education Sheets – Helen Marshall, Mallika Patel, and Susannah Koontz) before being critiqued and finalized by our committee as a whole. Although this year's annual meeting will not include a Best Practices session, we hope to share with meeting attendees an example of one of our first patient education sheets.

Two of our additional efforts have involved collaboration with the Program Committee. The first project has been the creation of "Oncology Boot Camp" – a half-day mini-symposium that will take place before our annual meeting and is aimed at providing a basic instructional series on supportive care practices to pharmacy students and residents as well as pharmacy practitioners new to the field of oncology. If you haven't already done so, check out the information detailing the Oncology Boot Camp offerings (www.hoparx.org/2010OncologyBootCamp.aspx) and pass the information along to your trainees and colleagues. And for those individuals unable to attend this year's annual meeting in New Orleans, our second collaboration with the Program Committee may be of interest to you – a "virtual meeting." Although the structure and execution of this program continue to be determined, we are looking to capture some education sessions for posting on HOPA University (HOPA U). So stay tuned for more details on this exciting offering!

Finally, by now you should have received your HOPA University clips. We hope you enjoy this small gift from our committee to help remind you of the many timely education offerings that HOPA U (www.hopaU.org) has for you. And remember, many of HOPA U's offerings are free, so be sure to share a clip with a colleague to spread the word. We look forward to seeing you in New Orleans to tell you more about all the work our committee has done and what we have planned in the coming year!

## Membership Committee

*Stephanie Sutphin, Chair*
*Karen Smethers, Vice-Chair*

Membership Committee members have been busy over the past several weeks reviewing applications for travel grants for the 2010 HOPA Annual Meeting in New Orleans. There were 89 travel grant applications submitted this year, including 52 trainee applicants. The decisions have been made, and HOPA awarded twenty $500 travel grants this year. Thank you to everyone who applied!

As the time for membership renewal approaches, don't forget about the many membership options available. The 2-year membership enrollment includes a 5% discount and is available to current members that renew for 2 years at a time. New members joining for 2 years will receive an additional incentive discount off their membership dues. The Recruit a Colleague program is also available to current members. You will receive $10 off of your membership renewal for each new member you refer to HOPA (up to a maximum of $30/year or $60/2-year renewal). Also, our group discount is still available to eligible institutions with 10 or more people joining or renewing HOPA memberships. Please call 877-467-2791 for details about the group discount.

The Membership Committee, in an effort to promote technician membership, is preparing a Q&A session with Jeanne Anderson, the 2009 HOPA Technician of the Year. Look for this article in an upcoming issue of *HOPA News*.

Lastly, the Membership Committee will again be doing the photo loop at the 2010 Annual Meeting. Please submit photos of you or your colleagues in the work environment by accessing the following link (www.hoparx.org/PhotoUpload.aspx). Be sure to include both name(s) and institution(s) on the photo or in the file name. We are looking forward to seeing all our members in New Orleans!

## Nominations & Awards Committee

*Susie Liewer, Chair*
*Karen Fancher, Vice-Chair*

The Nominations and Awards Committee would like to congratulate the following HOPA members who have been chosen to receive 2010 HOPA recognition awards:

- **HOPA Award of Excellence:** Val R. Adams, PharmD, FCCP, BCOP; University of Kentucky College of Pharmacy
- **Technician Award:** Therese McGrain, CPhT; Biologics, Inc.
- **New Practitioner Award:** LeAnn Best Norris, PharmD, BCPS, BCOP; South Carolina College of Pharmacy
- **Basic Science and Clinical Research Literature Award:** LeAnne Kennedy, PharmD, BCOP; Wake Forest University Baptist Medical Center
- **Oncology Pharmacy Practice Literature Award:** Brian Crandell, PharmD, BCOP, Duke University

Many qualified candidates were nominated for these awards and the selection process was very difficult. HOPA will honor all of the award winners during the 2010 Annual Meeting in New Orleans. The award presentation will take place on Wednesday, March 24.

## Professional Affairs Committee

*R. Donald Harvey, Chair*
*Marjorie Curry, Vice-Chair*

**Booth Development:** A detailed proposal from 3 vendors that included cost, construction, graphics, and storage information was sent to the Board for review and feedback. Following review,

# COMMITTEE UPDATES (CONTINUED)

we were asked to provide a single recommendation and expand details of the proposal, including meeting logistics. The committee is currently conducting an online vote for the optimal booth, with a plan to submit final recommendations to the Board within the month.

**Policies and Procedures:** We have been asked to develop two policies and are actively collaborating with other committees (Membership, Education, Finance) to develop an advertising policy that will dictate frequency, audience, budget, and venue. If you have recommendations or input, please contact Ginna Tucker. We are also continuing to develop a Guideline Endorsement policy that will serve to guide the process for rigorously reviewing and recommending clinical practice guidelines from other organizations.

**Interest Groups:** For the annual meeting, we will have three standing Professional Interest Groups that will meet each year: Pediatrics, BMT, and Technicians. Up to three other ad hoc groups will be defined on a year-by-year basis. If you have ideas or recommendations for interest groups and/or facilitators for this year's meeting, please let Donald Harvey know.

## Program Committee

*Daisy Yang, Chair*
*Gene Wetzstein, Vice-Chair*

The 6th Annual HOPA Meeting, scheduled for March 24-27 at the New Orleans Marriott, is almost here. To kick off the meeting, this year's keynote lecture on Healthcare Reform will be given by respected oncologist and national authority on healthcare policy, Dr. Joseph Bailes. In addition, HOPA 2010 will feature presentations covering a variety of interests, including clinical, technical, administrative, and practice issues. Over 20 hours of programming are scheduled over the 4 days, including BCOP lectures, plenary sessions, and workshops. Plenary sessions will feature significant papers, new drug updates, as well as updates from recent hematology-oncology conferences. Also, the popular Controversies in Care series is back again this year and will feature 6 case presentations and 2 debates.

Important notes about HOPA 2010:

- An Oncology Boot Camp is scheduled on March 24th, prior to the official start of the meeting. This workshop is appropriate for new practitioners and pharmacists who not focus solely on oncology, and it requires a separate registration.
- The Professional Affairs Interest Group meetings are scheduled for Friday from noon to 1:00 pm. Technicians, pediatrics, and bone marrow transplant are among some of the topics for the interest groups this year.
- Committee meetings are scheduled for Saturday afternoon after the official close of the meeting.
- To continue our efforts to go green, preprinted slide binders will **NOT** be provided to attendees. Slide presentations will be available on HOPA University for attendees to print out prior to the conference. Instructions will be e-mailed to all who are registered for the meeting as soon as the slides become available sometime in March.
- The meeting/speaker evaluation and self-assessment questions will also be available on HOPA University for print out before the meeting. It is recommended that these documents be completed as each session is attended to facilitate your online entry of your answers. Both the evaluation and questions must be completed and submitted in order to obtain continuing education credit.
- As a result of feedback from last year's attendees, a conference bag will **NOT** be provided this year.
- Regular meeting registration ended March 12 and will reopen onsite on March 23.
- Up-to-date conference information is posted on the HOPA website (www.hoparx.org/Hopa2010.aspx).

Hope to see you all in New Orleans!

## Publications Committee

*Amelia Chan, Chair*
*Melanie Brooke Bernhardt, Vice-Chair*

**HOTopics Discussion Forum:** HOTopics is a new quarterly series of interactive webinars from the HOPA Publications Committee that is for HOPA members only. The first HOTopics Forum will be held on Wednesday, April 28 or Wednesday, May 12 at noon PST. The topic is "Dosing of Cancer Drugs In Special Populations (eg, obesity, cachexia, and low serum creatinine)," and discussants will be Robert Ignoffo (Panel Chair), Sharyn Baker, and Jon Herrington. The first 20 members to sign up for the webinar will be given access to the web conference and reading materials. Look for an invitation from HOPA about this exciting new program!

## Standards Committee

*Theresa Mays, Chair*
*Myke Green, Vice-Chair*

The HOPA Standards Committee has been busy in its inaugural year. This committee has chosen to address an issue that oncology pharmacists worldwide face every day: dosing of anticancer agents in renal dysfunction. Beyond simply recapitulating dosing information from drug information resources, our committee is mining the medical literature to critically assess data and provide recommendations for dosing. Once evaluation of the data is completed, this information will be collated into a "white paper" for publication with the stamp of approval from HOPA. This project is moving along at a fast pace, but will not be finished in time for the HOPA 2010 Annual Meeting in March. This means there is still time to join this committee and be a part of this important project. Additionally, the HOPA Standards Committee will be working on one or more of the following projects in the next year: dosing of anticancer agents in hepatic dysfunction, vinca alkaloid administration and/or position statement on use and place in therapy of Totect®.

# DRUG UPDATES

## Measuring Anti-Drug Targets in Tumor Tissue

*Stacy S. Shord, PharmD, BCOP, FCCP*
*Clinical Pharmacology Reviewer*
*U.S. Food and Drug Administration*

**NOTE: The opinions and information in this review article are those of the author, and do not represent the views and/or policies of the U.S. Food and Drug Administration.**

Intensive research has focused on understanding interindividual differences in genetic sequences of common drug-metabolizing enzymes. The functional effects of the genetic variations in drug-metabolizing enzymes are a readily recognized phenotype described by changes in key pharmacokinetic parameters. Whereas the literature describing these functional effects contains key replicated findings, the literature describing drug transporters and targets pales in comparison, with fewer replicated findings. However, the contribution of these transporters and targets to the distribution, elimination, and the overall therapeutic response is well understood, and the completion of studies examining the genetic association of interindividual differences in these parameters is growing, including a focus on understanding the pharmacogenomics of anti-cancer drug targets.

In the Summer 2009 HOPA newsletter, the definitions, common study designs, and current laboratory methodology used to identify genetic variants in drug metabolism, transport, and target proteins were reviewed. The terminology, common study designs, and laboratory methodology can be applied to the examination of genetic variants in tumor tissue; however, the examinations look to identify somatic DNA mutations, since cancer cells undergo a series of **somatic mutations** (changes in DNA sequence that occur after conception) and the DNA sequence differs from **genomic DNA** (DNA sequence that occurs at conception). The purpose of this article is to introduce additional terminology and methodology used to examine interindividual differences in genetic sequences of common target proteins of anti-cancer drugs, such as vascular endothelial growth factor receptor (VEGF) and epidermal growth factor receptor (EGFR). Of note, tumor tissue may be paraffin-embedded tumor tissue or fresh-frozen tumor tissue. The tissue preparation can impact the methodology selected to detect the genetic variants, but will not be discussed further.

As a review, DNA is transcribed in the nucleus to **messenger RNA (mRNA)**. mRNA contains the "blueprint" for proteins. After mRNA is transcribed in the nucleus, it can be transported into the cytoplasm and translated by a ribosome. The transcribed **nucleotide bases** are grouped into **codons** (a group of three nucleotide bases). Each codon encodes for a specific **amino acid** with the exception of the **stop codons** that terminates protein synthesis. **Transfer RNA (tRNA)** and **ribosomal RNA (rRNA)** facilitate the translation of the protein by mediating recognition of the codons and providing the correct amino acids as the protein is being translated. These somatic DNA mutations are identified using standard molecular biology techniques including assays to sequence DNA, identify specific gene sequences or measure mRNA or protein expression.

As discussed in the Summer 2009 publication, variants in DNA sequence may be detected using **polymerase chain reactions (PCR)** followed by **restriction fragment length polymorphism (RFLP)**, **tagged probes** or **fluorescent dyes**, or by **sequencing**. These methods are also used to detect somatic mutations located in the DNA isolated from malignant tissue. For example, EGFR mutations located in **exons** 18-21 can be detected using one of these laboratory methods.[1] The activating mutations within these exons appear to correlate with increased sensitivity to the small molecule inhibitors of the EGFR tyrosine kinase.[2] Other mutations that may be detected using these methods include mutations in the ***KRAS*** (Kirsten-ras) gene and the ***bcr-abl*** (breakpoint-cluster region-Abelson leukemia-virus protein) gene. As you are aware, the *KRAS* **wild-type** (most common sequence of a gene) gene expression is associated with improved outcomes in patients receiving panitumumab and cetuximab in colon cancer.[3,4] As for the *bcr-abl* gene, these methods are used to detect the specific mutations in the gene that may be associated with clinical resistance to imatinib and help direct subsequent therapy.[5]

An alternative molecular biology technique commonly used to identify the expression of a variant gene is called **fluorescence *in situ* hybridization (FISH)**. This method uses fluorescent probes to detect the presence or absence of the desired gene (or mRNA) sequence. The probe binds to the desired DNA sequence and fluorescence microscopy is used to visualize if the desired sequence is absent or present and/or identify the number of chromosome copies within the tumor tissue. The "strength" of the membrane staining can be semiquantitated by counting the total number of copies of the desired gene found in a standard number of cells and dividing by the number of copies of a reference gene in the same number of cells. FISH is used to diagnosis diseases, such as Down's syndrome, or detect chromosomal rearrangements, such as the Philadelphia chromosome [aka t(9:22)]. FISH is also commonly used to detect **HER-2** amplification in malignant breast tissue; it is often used to confirm HER-2 overexpression when the protein expression is uncertain. Gene amplification of the drug target **EGFR** may be identified in malignant non–small-cell lung cancer and colon cancer tissue by FISH and it appears to be a sensitive predictor of the objective response in clinical trials.

In the laboratory, mRNA expression is measured using a Northern blot or **reverse transcription polymerase chain reactions (RT-PCR)**. The more traditional method to quantitate mRNA levels

# DRUG UPDATES (CONTINUED)

is the Northern blot. The RNA is extracted and the fragments are sorted by size using gel electrophoresis. The fragments are then transferred to a membrane and labeled probes specific for the RNA fragment of interest are hybridized to the membrane. The hybridization probes are detected using **autoradiography** (image transferred to radiographic film) and the RNA "band" is semiquantitated using **densitometry** (a quantitative measurement of optical density). A newer molecular biology technique is the use of **real-time RT-PCR** to measure mRNA levels. Basically, the RNA strand is reverse transcribed to create a **complementary DNA (cDNA)** strand. The cDNA is then amplified using PCR, and the PCR products are then detected in real time using fluorescent signals, probes, or beacons to quantitate the RNA using a standard curve or copy number calculation. These methods may be used in addition to FISH to detect the *bcr-abl* gene.[6]

The protein product may also be measured in tumor tissue. Proteins are measured using Western blot or immunohistochemistry (IHC). A **Western blot** uses principles similar to the Northern blot. The protein is extracted and separated by size using gel electrophoresis. The protein is then transferred to a membrane and the membrane is probed with antibodies specific to the desired protein. The antibodies can be detected on film and the protein "band" is measured by densitometry. A more common method used to measure protein in tumor tissue is called **IHC**. This method employs tagged antibodies to determine the absence or presence of a protein in the tissue. The protein expression is graded or measured using the tag. For example, commercial kits are now available to measure **HER-2** and **EGFR** protein levels that are commonly overexpressed in specific solid tumors. These kits employ IHC to quantify the amount of these proteins in tumor tissue and provide guidance to the selection of anti-cancer drugs in women with breast cancer and patients with non–small-cell lung cancer. These kits permit the calculation of the percentage of tumor cells with perceptible membrane staining with the tagged antibody, and the percentages are grouped into four individual scores ranging from zero to 3+. Although IHC testing for HER-2 in breast cancer tissue demonstrates clinical utility, this test for EGFR in head and neck, lung, and colon cancers is not recommended.

In summary, many standard laboratory techniques, including FISH and IHC, are commonly used to measure gene amplification and protein expression in tumor tissue. Other methods, including DNA sequencing using PCR followed by the use of tagged probes or fluorescent dyes or by direct sequencing, can be used to identify somatic DNA mutations within the tumor tissue. These methods are used to identify common anti-cancer targets, such as **HER-2**, **EGFR**, **bcr-abl**, and **KRAS** and help guide treatment selection in various solid tumors and hematologic malignancies. This review will hopefully facilitate an understanding of the different laboratory methods used to identify somatic DNA mutations and permit a greater appreciation of the correlations identified in the primary literature.

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# DRUG UPDATES (CONTINUED)

## Ofatumumab (Arzerra™)

**Class:** CD20-directed cytolytic monoclonal antibody.

**Indication:** Treatment of chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab.

**Dose:** Twelve doses should be administered as an IV infusion as follows: 300 mg initial dose, followed 1 week later by 2,000 mg weekly for 7 doses, followed 4 weeks later by 2,000 mg every 4 weeks for 4 doses.

**Adverse event prevention:** Premedicate 30 minutes to 2 hours prior to each dose with oral acetaminophen 1,000 mg, oral or intravenous antihistamine (cetirizine 10 mg or equivalent), and intravenous corticosteroid (prednisolone 100 mg or equivalent).

**Dose modifications:** Infusion should be interrupted for infusion reactions of any severity. For grade 4 infusion reactions, the infusion should not be resumed. For grade 1, 2, or 3 infusion reaction, if the infusion reaction resolves or remains less than or equal to grade 2, the infusion may be restarted with the following modifications according to the initial grade of the infusion reaction.

*Grade 1 or 2:* Infuse at one-half of the previous infusion rate.

*Grade 3:* Infuse at a rate of 12 mL/hour.

**Adverse events:** Most common (≥10%): neutropenia, pneumonia, pyrexia, cough, diarrhea, anemia, fatigue, dyspnea, rash, nausea, bronchitis, and upper respiratory tract infections. Serious adverse events include neutropenia, pyrexia, and infection (including pneumonia and sepsis).

**Drug interactions:** No formal drug-drug interactions have been conducted with ofatumumab.

## Ofatumumab in Refractory Chronic Lymphocytic Leukemia (CLL)

*Melissa Pozotrigo, PharmD*
*Oncology Pharmacy Practice Resident*
*Memorial Sloan-Kettering Cancer Center*

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in Europe and North America.[1] It is characterized by the accumulation of immature B lymphocytes in the blood, bone marrow, and lymphatic tissues. The American Cancer Society estimates about 15,490 new cases of CLL and about 4,390 deaths from CLL in the U.S. in 2009.[2] Initial presentation of CLL is variable, with some patients presenting with an indolent leukemia with a long survival and others experiencing aggressive disease with early and frequent need for treatment.[3]

The treatment for CLL involves an individualized approach and should be tailored according to the patient's age, performance status, prognostic factors, and clinical manifestations. In patients who are asymptomatic, treatment is oftentimes deferred until the patient begins experiencing symptoms, which may include enlarged lymph nodes, fevers, night sweats, weight loss, and recurrent infections.

Once a patient becomes symptomatic and treatment is warranted, various options exist. Agents that have exhibited activity against CLL include deoxyadenosine nucleoside analogues such as fludarabine or cladribine, alkylating agents such as chlorambucil or cyclophosphamide, monoclonal antibodies such as rituximab or alemtuzumab, and/or combination chemotherapy such the fludarabine-cyclophosphamide (FC) regimen. While chlorambucil has traditionally been the mainstay of therapy, more effective disease control has been observed when combining fludarabine with chemoimmunotherapy such as rituximab or alemtuzumab. Three drug combination treatments have also been studied in CLL. Fludarabine or pentostatin has been evaluated in combination with cyclophosphamide and rituximab.[4,5] While these regimens have proven to be beneficial with regards to their clinical efficacy, they also have greater toxicity versus monotherapy with their individual counterparts and therefore may not be suitable for all patients. Other treatment modalities for CLL are radiation therapy and bone marrow or peripheral stem cell transplant. Lastly, patients who have relapsed or refractory disease may be referred for enrollment into a clinical trial.

While advances in the treatment of CLL have improved initial overall response (OR) rates, complete response (CR) rates, and progression free survival (PFS), CLL remains incurable with standard therapies. Patients inevitably relapse, becoming increasingly refractory to treatment, and often acquiring high-risk chromosomal abnormalities such as del(11q22) and del(17p13).[6]

It has been documented that less than 25 percent of patients with refractory CLL respond to most current treatments, thus emphasizing the need for novel therapies in this patient population.[7] As previously mentioned, monoclonal antibodies are a class of drugs that have shown to be active in the treatment of CLL. The newest agent in this class of drugs, ofatumumab, is a fully humanized, high-affinity IgG1k monoclonal antibody.[8] It exerts its action by binding to both the small and large extracellular loops of the CD20 molecule, which is expressed on normal B lymphocytes (pre-B- to mature B-lymphocyte) and on B-cell CLL. It differs from rituximab in that it has a higher affinity for CD20, activates complement-dependent cytotoxicity more effectively, and is superior in killing B-cell lines with low CD20 expression. An initial phase I/II study in 33 patients with relapsed CLL giving weekly therapy for 4 week showed a 50% OR.[9] Based on results from the pivotal phase II study conducted by Osterberg and colleagues, ofatumamab received FDA approval in October 2009 for the treatment of patients with CLL refractory to fludarabine and alemtuzumab.[10]

The efficacy and safety of ofatumumab was assessed in a single-arm, open-label, multicenter, international trial in 154 subjects with fludarabine-refractory CLL. Patients were classified as fludarabine

# DRUG UPDATES (CONTINUED)

## Ofatumumab (Arzerra™)

and alemtuzumab refractory (FA-Ref) or bulky fludarabine refractory (BF-Ref) and were treated with a total of 12 intravenous infusions of ofatumumab. Objective response was recorded by investigator assessment and by an independent review committee (IRC). In this prespecified interim analysis, 42% of patients in FA-Ref group and 34% of patients in the BF-Ref group responded to single-agent ofatumumab (investigator assessment); response rate by IRC assessment was 58% in the FA-Ref group and 47% in the BF-Ref group. Median time to response was 1.8 months in both groups, and median duration of response were 7.1 months and 5.6 months in the FA-Ref and BF-Ref groups, respectively.

The most common drug-related adverse events reported (frequency ≥5%) were neutropenia, rash, urticaria, fatigue, chills, diarrhea, pyrexia, pneumonia, dyspnea, cough, nausea, hyperhidrosis, anemia, pruritus, and hypotension. The investigators reported that all analyses were negative for human antihuman antibodies (HAHA). All cases of neutropenia were recorded during the pivotal clinical trial for ofatumumab, and of 108 patients with normal neutrophil counts at baseline, 45 (42%) developed ≥ grade 3 neutropenia. Grade 3 and 4 cytopenias were reported with ofatumumab, leading to the recommendation for regular monitoring for cytopenias.

Treatment with ofatumumab consists of a total of 12 intravenous infusions over a period of 24 weeks.[8] Eight weekly IV infusions are administered, followed by four monthly infusions. The initial dose is 300 mg, with subsequent infusions dosed at 2000 mg. To prevent infusion related reactions, patients should be premedicated 30 minutes to 2 hours prior to each infusion with oral acetaminophen (1000 mg or equivalent), oral/IV cetirizine (10 mg or equivalent), and an IV corticosteroid (prednisolone 0-100 mg or equivalent). Doses should be interrupted and/or modified appropriately for infusion related reactions.

Ofatumumab is available as a preservative-free liquid for dilution and intravenous administration at a concentration of 20 mg/mL.[8] Vials should be stored in the refrigerator until use and protected from light. The vials are designed for single use only. During therapy, patients should be monitored closely for cytopenias. Complete blood count and platelet counts should be checked at regular intervals during therapy, with an increase in the frequency of monitoring in patients who develop grade 3 or 4 cytopenias. Additional warnings and precautions for this agent include infusion reactions, progressive multifocal leukoencephalopathy, and hepatitis B reactivation.

Based on the available literature, ofatumumab has shown positive results in CLL, which has motivated researchers to investigate the use of this agent in earlier stages of the disease.[11] A phase III study of ofatumumab in combination with fludarabine and cyclophosphamide for patients with CLL as second-line treatment is currently enrolling patients. The open-label study will randomize 352 patients to evaluate PFS of ofatumumab in combination with FC therapy versus FC therapy alone for the treatment of relapsed CLL.

Another front-line trial studying ofatumumab in CLL is a phase III study evaluating ofatumumab combined with chlorambucil in patients with previously untreated CLL.

In addition to the use of this agent in CLL, ofatumumab also suggests possible activity in other malignancies such as non-Hodgkin's lymphoma (NHL). An ongoing phase II study will assess ofatumumab in patients with Waldenstrom's macroglobulinemia, a rare type of slow-growing NHL.[12] Another phase II study in lymphoma is evaluating ofatumumab plus ICE or DHAP chemotherapy regimen in relapsed/refractory diffuse large B-cell lymphoma (DLBCL). Lastly, the use of ofatumumab is also being explored in areas outside of oncology, including rheumatoid arthritis and multiple sclerosis.

In summary, ofatumumab is a highly specific anti-CD20 monoclonal antibody that received accelerated FDA approval for use in patients with CLL that is refractory to fludarabine and alemtuzumab. The approval of this agent was based primarily on data from a single-arm, multicenter study of 154 patients. Results demonstrated that treatment with ofatumumab yielded an investigator-determined overall response rate of 42%, with a medium duration of response of 6.5 months. No complete responses were observed. Publication of the results of the pivotal study leading up to the approval of ofatumumab is not yet available. Ofatumumab may offer an alternative therapy for patients with CLL refractory to fludarabine and alemtuzumab, but given its high cost, further studies should be considered to establish its role in therapy in comparison with rituximab.

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# DRUG UPDATES (CONTINUED)

## Pazopanib (Votrient®)

**Class:** Multikinase angiogenesis inhibitor.

**Indication:** Treatment of advanced or metastatic renal cell carcinoma.

**Dose:** 800 mg once daily.

**Dose adjustments:** Initiate at 200 mg daily in moderate hepatic impairment, do no use in severe hepatic impairment (bilirubin >3 x ULN with any ALT level). ALT >3 to 8 x ULN: continue treatment, monitor LFTs weekly. ALT >8 x ULN: hold therapy until LFTs return to baseline; consider reinitiation at <400 mg daily. Discontinue treatment if development of grade 4 proteinuria, or persistent hypertension uncontrolled on therapy.

**Common adverse effects:** Hypertension, fatigue, hair color change, nausea, diarrhea, anorexia, electrolyte disturbances, and LFT elevations.

**Serious adverse effects:** Arterial thrombotic events, QT prolongation & torsades de pointes, GI perforation/fistula, hemorrhaging, hypothyroidism, and proteinuria.

**Drug interactions:** CYP 3A4 inhibitors and inducers (consider dosage adjustment when concomitant therapy is required.)

## Pazopanib in Renal Cell Carcinoma

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Renal cell carcinoma (RCC) accounts for 2%-3% of all malignancies, with a median age at diagnosis of 65 years. Though the reason is unknown, there has been a steady 2%-3% increase in RCC incidence per year for the past 20 years.[1] It is the eighth most commonly diagnosed cancer overall and the third most commonly diagnosed genitourinary malignancy, after prostate and bladder cancer. Smoking and obesity are attributed to an increased risk for the development of RCC, but hereditary abnormalities, such as mutations in the Von Hippel-Lindau (VHL) gene, provide additional predispositions to development of RCC. The most common histologies of RCC is clear cell type, which accounts for 75% of all cases, and papillary type, which accounts for about 15% of all cases.[2-3]

The most common signs and symptoms associated with RCC include gross hematuria, flank pain, and the presence of a flank mass. Unfortunately, 91% of patients are asymptomatic at diagnosis and 39% of patients present with locally advanced or metastatic disease at presentation. Five-year survival rates for patients with advanced and metastatic disease ranges from 69% to 23%.[4]

Patients with stage I-III or resectable stage IV according to the TNM staging system for RCC should have their lesions removed by either radical or partial nephrectomy. In early-stage disease, this provides the highest rates of possible cure and helps to alleviate symptoms in advanced-stage and metastatic disease. Systemic treatment options for advanced, metastatic, or recurrent disease were limited until the advent of cytokine novel targeted therapy. Interferon treatment and high-dose interleukin-2 therapy provided high response rates and remission in some patients. Recently targeted agents, including sorafenib, sunitinib, pazopanib, temsirolimus, everolimus, and bevacizumab in combination with IFN have been approved for treatment of advanced RCC.[5]

Pazopanib (Votrient®) is a multikinase angiogenesis inhibitor. It inhibits tumor growth by inhibiting cell surface vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, VEGFR-3), platelet-derived growth factor receptors (PDGFR-alpha and -beta), fibroblast growth factor receptor (FGFR-1 and -3), cytokine receptor (cKIT), interleukin-2 receptor inducible T-cell kinase, leukocyte-specific protein tyrosine kinase (Lck), and transmembrane glycoprotein receptor tyrosine kinase (c-Fms).[6] Pazopanib received FDA approval on October 19, 2009 for treatment of patients with advanced RCC.

The safety and efficacy of pazopanib was compared with placebo in a randomized, phase III, multicenter open-label trial (VEG105192).[7] Patients with advanced-stage clear cell RCC and measurable disease with no prior treatment or 1 prior cytokine-based treatment, were stratified and randomized (2:1) to receive pazopanib 800 mg or placebo. Primary endpoint of progression free survival (PFS) & secondary endpoints of overall survival (OS) and safety were evaluated.

A total of 233 treatment naïve and 202 cytokine pretreated patients were enrolled (290 pazopanib; 145 placebo). PFS was significantly prolonged with pazopanib in the overall study population (9.2 vs. 4.2 months; $P < .0000001$), in treatment-naïve patients (11.1 vs. 2.8 months; $P < .0000001$), and in cytokine pretreated patients (7.4 vs. 4.2 months; $P < .001$). RR was 30% with pazopanib vs. 3% with placebo, and median duration of response was 7.4 months with pazopanib vs. 3.8 months with placebo.

Side effects that are most commonly seen with pazopanib therapy include diarrhea, hypertension, hair color change, nausea, anorexia, and vomiting. Prior to initiation of treatment, blood pressure should be well controlled and maintained at normal levels with appropriate antihypertensive therapy. Elevations in liver function tests and hepatotoxicity also commonly occur with pazopanib therapy, and this has been seen in up to 53% of patients. Therapy-related hypothyroidism can also be seen, and thus routine monitoring of thyroid function tests is recommended. As with all VEGF inhibitors, the risk of bleeding and hemorrhagic events is also consistent. In randomized clinical studies, all-grade hemorrhagic events were up to 16%. Rare cardiotoxicity characterized by QT prolongation, torsades de pointes, and arterial thrombotic events has also been seen in 3%-5% of patients.[8-9]

# DRUG UPDATES (CONTINUED)

## Pazopanib (Votrient®)

Pazopanib should be initiated at a dose of 800 mg once daily. The dose should be reduced in patients with underlying hepatic impairment (200 mg daily) or in patients who develop hepatotoxicity (400 mg daily) as a result of pazopanib therapy. Dose reduction may also be necessary in patients who receive concomitant treatment with strong CYP3A4 inhibitors and inducers, and grapefruit juice should be avoided. Pazopanib has not been studied in patients with CrCl <30mL/min, and therefore cautious use in this patient population is recommended, although formal dosage reductions are not recommended.

Additional clinical considerations for pazopanib therapy include discontinuation of agent with development of severe proteinuria (grade 4), hypertension (severe, persistent, and refractory to antihypertensives and dose reduction), and wound dehiscence. Temporary interruption of therapy is also suggested in patients undergoing surgical procedures.

Pazopanib currently serves as an additional therapeutic option for management of advanced renal cell carcinoma. Its multi-targeted mechanism of action provides additional anti-angiogenic and anti-tumor activity. In comparison with other targeted agents, specifically sorafenib and sunitinib, RR has been similar (5%-21% and 7%-40%, respectively) and PFS ranged from 5-14 months with both agents. It may also have a better toxicity prolife as compared to sunitinib.[10] A head-to-head study comparing sunitinib vs. pazopanib is currently being conducted in patients with advanced renal cell carcinoma, but as of yet a comparison with mTOR inhibitors (everolimus and temsirolimus) shown to have proven efficacy has not been conducted.

In conclusion, pazopanib is a multi-targeted kinase inhibitor approved for treatment of advanced and metastatic renal cell carcinoma. It is a viable therapeutic option for the treatment of advanced RCC and has been shown to have similar efficacy when compared to traditional therapy. Its oral route of administration and favorable safety profile may provide additional advantages. Further study evaluating pazopanib as an option in the front-line or adjuvant setting, as well as in combination with other active therapies with different mechanism of action (ie, mTOR inhibitors), needs to be conducted in order to evaluate full scope of efficacy and safety.

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