



HOPA News

HOPA 2009 in Miami a Success!



The numbers tell the story: 576 registrants, 551 total attendees (55 from outside the US), over 70 speakers, 20 workshops, 8 symposia, over 90 posters, plus 35 exhibits staffed by 177 industry representatives for a total of 728 participants. In addition, HOPA's first annual charity event, "Run From the Sun," a 5k run/walk for a local Miami patient advocacy group, raised \$5,000 for the Richard David Kann Melanoma Foundation of West Palm Beach, Florida.



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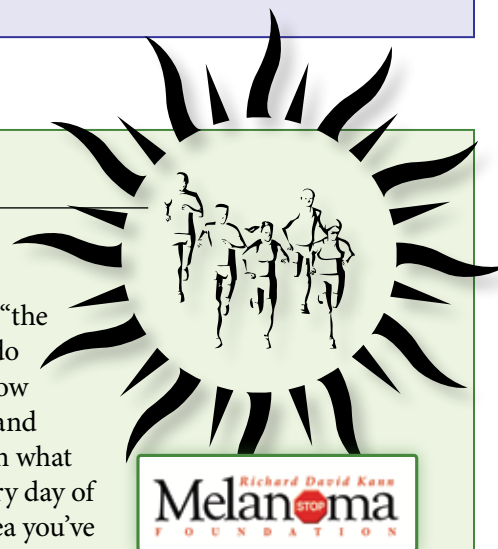
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HOPA's 1st Annual 5k Charity Event—"Run From The Sun"

Brandy Strickland, PharmD, Wake Forest University Baptist Medical Center

Miami, FL (June 20, 2009) – HOPA's first annual charity 5K "Run From the Sun" was a huge success. Debbie Kann Schwarzberg, founder of the Richard David Kann Melanoma Foundation, was the official race starter and also spoke at the Run/Walk Awards Ceremony. Debbie explained why the organization got started and the purpose of the foundation, "to give 110% of resources to school-based education and to the SunSmart America curriculum." Debbie also expressed her

gratitude and admiration for oncology pharmacy practice, stating that she has "the UTMOST respect for the work you all do and that your focus is in oncology. I know what it takes, I know how pharmacists and pharmacy techs make a big difference in what happens with a patient's life during every day of treatment, and I applaud you for the area you've chosen—and can only tell you that patients and organizations and families really do appreciate the work you do and how important you are."



(CONTINUED ON PAGE 2)

HOPA's 1st Annual 5k Charity Event *continued*

Debbie then presented the awards to the top 3 male and 3 female finishers.

The 5K began early in the morning, on the beautiful golf course at the Doral Marriott in Miami. There were 101 participants, \$5,000 was raised, and 78 people made donations. The top 3 men and women finishers were:

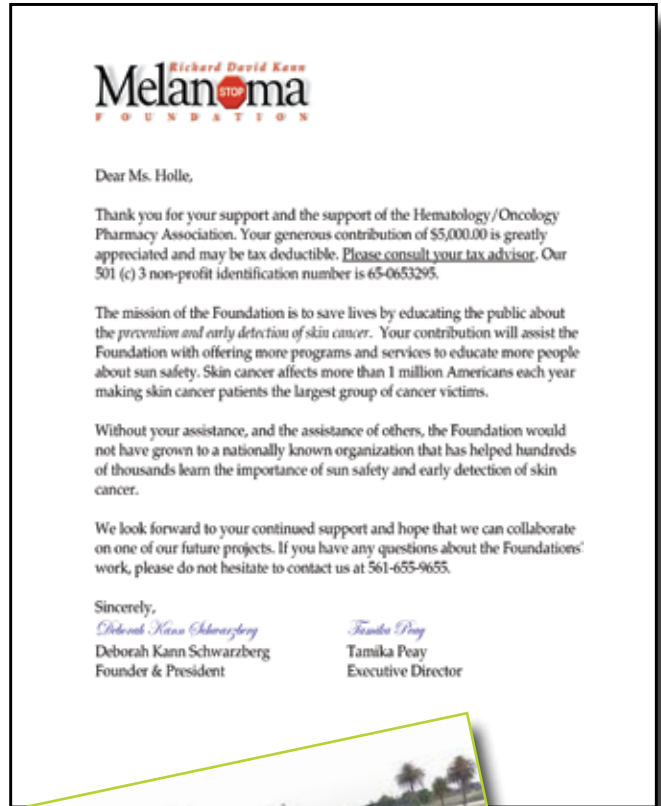
- Ryan Hull, 21:50
- Steve Williamson, 21:53
- Rick Sedlak, 21:56
- Brandy Strickland, 22:03
- Sarah Hudson-Disalle, 24:39
- Brigit Cloos, 24:44

Each runner received a goody bag at the end of the event that included a granola bar, juice, and a banana (donated by the Johns Hopkins Hospital Oncology Residency Program) and a sample of sunscreen (donated by Sun & Skin Care Research, Cocoa, FL) as well as a T-shirt.

HOPA was pleased to have the opportunity to work with and support the Richard David Kann Melanoma Foundation, and plans to continue to help raise awareness for skin cancer prevention. HOPA would like to thank the following members and others for their generous support of the Richard David Kann Melanoma Foundation and HOPA's 1st Annual 5K Run/Walk.

- | | |
|-------------------------|-------------------------|
| Violette Ajiboye | Cynthia Johnston |
| Ziba Ansari-Jaberi | Jeff Kaiser |
| Amal Arnaout | Alex Kardos |
| Gayle Blouin | Nancy Kavan |
| Betty Carpenter | LeAnne Kennedy |
| Maggie Charpentier | Susannah Koontz |
| Debra Chibroski | Andy Kurtzweil |
| Amanda Christman | Janet Laquet |
| Jordan Dawson | Debra Litwak |
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| Shrina Duggal | Anne McDonnell |
| DesignWrite | John McFarland |
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| Mandy Gatesman | Laura Michaud |
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| David Henry | Cindy O'Bryant |
| Teresa High | Donna O'Leary |
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| Amy Seung |
| Karen Smethers |
| Brad Stanford |
| Melissa Sterback |
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| Debra Tesoro |
| Jennifer Thompson |
| Katherine Tipton |
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| Jennifer Tobin |
| Scott Tyrrell |
| Casey Williams |
| Sol Yoder |
| Jennifer Ziegler |



Skin Cancer: Prevention & Early Detection

Brandy Strickland, PharmD, Wake Forest University Baptist Medical Center

Skin cancer affects more than 1 million Americans each year, more than all other cancers combined. Over 10,000 Americans die each year from melanoma, which is the deadliest form of skin cancer. If detected early, all forms of skin cancer are nearly 100% preventable and curable. Early detection and prevention is KEY in the fight against melanoma!! Important counseling points for patients include:

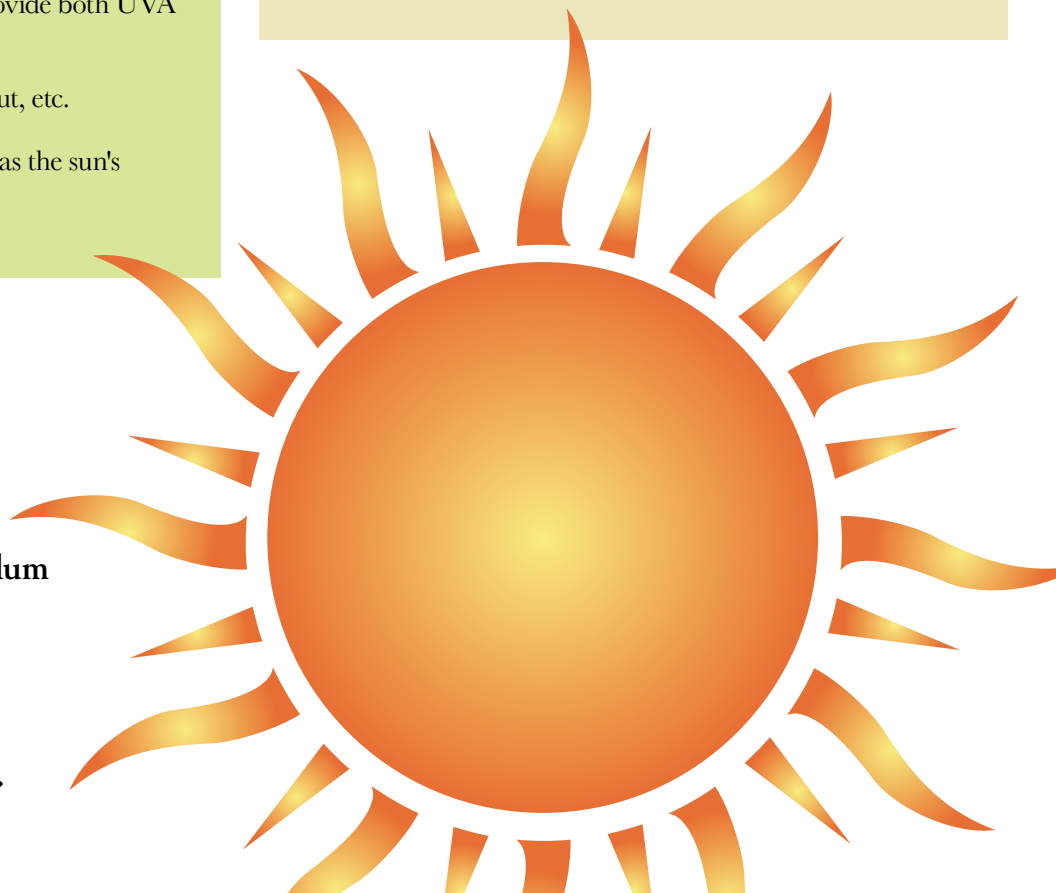
Prevention

- Avoid sun tanning or burning—both are dangerous and indicate skin damage that can lead to skin cancer. Even one or two serious sunburns before the age of 18 years old can double a person's chance of getting skin cancer later in life.
- When outside during the day, a comprehensive sun protection program includes:
 - Use a sunscreen with an SPF (sun protection factor) of at least 15 or more; apply 20 minutes before going outside and reapply frequently.
 - Wear a wide-brimmed hat to protect your face, neck, and ears.
 - Put on protective clothing such as tightly woven, light-weight fabric in the form of a long-sleeve shirt and pants.
 - Avoid direct sun between 10:00 AM and 4:00 PM, when the sun's rays are strongest.
 - Wear high quality sunglasses that provide both UVA and UVB protection.
 - Find shade—umbrella, tree, shade hut, etc.
 - Protect yourself even on cloudy days as the sun's burning UV rays still come through.

Early Detection

- Check your own skin on a regular basis. Look for any new spots, freckles or moles, or any changes in existing ones.
- Know what to look for on your skin: the ABCD rules of skin cancer:
 - A - asymmetry (one half doesn't match the other)
 - B - borders (any irregular or notched border, not smooth around)
 - C - color (most healthy moles or spots are one shade of brown; look for any variation in color including brown, black, white, pink or even blue)
 - D - diameter (anything that grows or is larger than a pencil eraser)
- See a dermatologist, a doctor who specializes in skin, on a regular basis starting in your teenage years and at the first sign of any new or different spot on your skin.

For more information about the SunSmart America™, a K-12 curriculum to promote skin cancer prevention and early detection, please contact the Richard David Kann Melanoma Foundation at 561-655-9655 or visit <http://www.melanomafoundation.com>.



Strategies to Prevent Cancer Chemotherapy Errors

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

Memorial Sloan Kettering Cancer Center dispenses 175,000 chemo doses a year through its network of 27 pharmacy satellites. These strategies have been extremely helpful to avoid cancer chemotherapy errors and you may want to consider them in your practice:

- Mandate the use of preprinted order forms that standardize practice and “force functions.”
- Implement prescribing guidelines and enforce them. Use full generic drug names; ban use of error-prone abbreviations such as “U” and “qd.”
- Ban verbal orders for the initiation of chemotherapy. Verbal orders for chemotherapy should only be allowable in the event of an acute adverse reaction.
- Work diligently to develop a computerized prescriber order entry system that is interfaced with the pharmacy and the electronic administration systems. Pharmacists should be integrally involved building the treatment order sets, establishing the maximum allowable doses, and training clinicians in all systems.
- Make drug and policy information available electronically and ensure all members of the team know how to use it. Develop drug treatment guidelines that may be unique to your practice and that include dose information, hydration and infusion guidelines, and antiemetic & supportive care information. Update as often as necessary.
- Ensure that critically important laboratory doses are available before drug dispensing and administration with real-time interfaces.
- Realize that errors can and will happen at your practice site, so create a culture of safety. Be supportive of pharmacists, nurses, and physicians who make errors. Provide professional counseling. Discuss all errors in a multidisciplinary environment where all involved parties can constructively discuss what can prevent a recurrence of a same or similar error. Have a formal process to report and trend all “near-misses.”
- Ensure that the pharmacy department is well-represented on the Institutional Review Board and all Hospital Quality and Clinical Committees. Create a positive relationship with the senior physicians and administrators to ensure that quality and safety always come before productivity.
- Distribute the Institute of Safe Medication Practices Medication Safety Alerts and the Joint Commission’s Sentinel Event Alerts to medical nursing, pharmacy, and quality improvement staff. Conduct formal educational programs on medication error prevention regularly, by reviewing actual errors that have occurred at your practice site (with demographic information redacted).
- Develop tools to assess the competency of new staff and annually assess and document the competency of existing staff.
- If chemotherapy orders are written or entered by oncology fellows or nurse practitioners, require that they be cosigned or validated by an attending physician before being considered valid.
- Consider ways to involve patients in your quality assessment and medication safety program.
- Assess the clarity of a manufacturer’s vial, syringe, and other labels to avoid confusion. Have a program to distinguish “look-alike, sound-alike drugs,” and employ judicious use of TALLman lettering in ordering, labeling and administration systems (eg, vinCRISTine and vinBLASTine).

COMMITTEE UPDATES

Update from the Board

Much Work to Do in a Shortened Organizational Year

Jane Pruemmer, PharmD, BCOP, At-Large Board Member

How much can we accomplish in the next 9 months? With the Annual Meeting occurring in March 2010, the HOPA Executive Board, along with all of its vital committees, is keeping extremely busy this summer. The Executive Board hopes that HOPA members have taken the opportunity to log onto the HOPA website (www.hoparx.org) to stay up to date on the latest happenings of the organization. In our ongoing commitment to keep our members informed, the Board would like to summarize some of the key happenings here. With the approval of the updated HOPA By-Laws by the membership, we have further delineated various roles of our membership within the organization. Other exciting areas of communication to you, our members, include the work of our 11 standing committees within the organization (see committee updates below). A significant amount of work has been done to keep HOPA moving toward meeting its goals, which are your goals. Additionally, the Board is working together with the committees to develop policies and procedures to facilitate a smooth transition from year to year. We now have policies on committee membership, use of the HOPA Listserv, and other organizational policies. Just talk to some of our Board members and committee leadership about how busy everyone has been, developing further structure for our organization. Since we are still a fairly young organization, we have come to recognize the need for improved communications and a more complete framework for how we function. So, hopefully, all members will have a clearer picture of HOPA, and their roles as active members within it.

We encourage you to spend a few moments to check out the Members Only section of the HOPA website, and review the new policies and procedures that apply to you. Also, it's never too early to begin your personal plan to participate in the Annual meeting in March. A new feature for highlighting the research-in-progress of our trainees is being planned, and our Program Committee and BCOP Recertification Committee have been already identifying topics and speakers for a truly intense 2010 educational meeting. The Board sincerely appreciates the efforts of all of our members in contributing to HOPA to make it successful!

HOPA Members in All 50 States

With the recent addition of a member in Wyoming, HOPA for the first time has members in all 50 states and Washington, DC. Thanks to Dr. Cara Harshberger, Coordinator of Experiential Education at the University of Wyoming School of Pharmacy, for becoming our first Wyoming member!

BCOP Recertification Committee

The BCOP Recertification Committee is responsible for the 6 recertification hours provided at the HOPA Annual Meeting, and these lectures are repeated at the ACCP Annual Meeting and at the ASHP Midyear Meeting. This responsibility includes identifying topics and reviewing the speakers' presentations, ACPE continuing education self-assessment questions, and BCOP Recertification assessment questions. The topics are selected based on areas of oncology that have novel concepts or therapeutic strategies and cover all 4 domains required for examination content set forth by BPS, the Board of Pharmaceutical Specialties. This past year the committee created a formalized process that all three pharmacy organizations are using to validate the questions used for BCOP Recertification assessments for the home syllabus, the review course, and the "live" sessions.

Currently the committee is in the midst of finalizing the six presentation topics and inviting faculty for the "live" portion of the 2010 recertification. Additionally, the group is actively evaluating the process of question validation that was implemented for the assessment for the "live" CE sessions and the other recertification options.

COMMITTEE UPDATES (CONTINUED)

Membership Committee

Our committee is off to a great start this year, welcoming back 6 former members and introducing 8 new members. Stephanie Sutphin, this year's chair, along with vice chair Karen Smethers, are prepared for a productive committee year. The Membership Committee's focus, aside from member recruitment and retention, is on successful programs such as the Annual Meeting Travel Grants and administration of member surveys. While the committee has successfully increased membership over the years, this year's special focus will be on recruiting technician members as well as new practitioner initiatives.

New this fall is a special "New Member Discount" initiative. Renewal date for membership begins on April 1 each year. This year, if a new member joins from September thru March, and chooses 2-year membership, a 25% discount will apply to the normal rate. This is to help encourage those who wish to join but hesitate due to the lateness in the year. Check our website soon for more details.

The committee wishes to thank all our members who participated in the member photo loop at our annual meeting in Miami. We hope to do this again at next year's annual meeting in New Orleans. This was a great opportunity to connect the names and faces and to get to know our HOPA members.

Nominations & Awards Committee

This year the Nominations & Awards Committee has expanded its membership to 10 members. The committee welcomes new members Bradi Frei, David Baribeault, Dawn Colburn, and Sara Gressett. This summer the committee is very busy soliciting nominations for the 2010 HOPA awards. The HOPA award winners will be presented at the annual HOPA conference, which will be hosted March 24-27 in New Orleans, Louisiana.

Our next mission is setting the slate for the Executive Board elections. The call for nominations for the HOPA Executive Board will open in September 2009. The new By-Laws approved this spring expanded the number of Member-at-Large positions. Start thinking about who you would like to nominate for the President-Elect, Treasurer, and Member-at-Large positions. The elections will open in January 2010.

Professional Affairs Committee

We continue to evaluate opportunities for collaborations with other organizations, with HOPA and APhA co-sponsorship of educational monographs for community pharmacists in breast (2) and lung cancer in the works. Thanks to committee members Dan Zlott, Ginna Tucker, and Brad Burton, we are evaluating a booth presence for HOPA at select annual meetings. Also, be on the lookout for an electronic survey on CE interest for the American Society of Hematology (ASH) annual meeting, jointly developed by Patti Halterman and the Survey Subcommittee of the Membership Committee.

Publications Committee

HOTopics Forum: The Publications Committee voted to move forward with plans to use a quarterly webinar format to discuss topics of major interest in oncology, including important papers in the oncology literature regarding the management of cancer patients. The first webinar is planned to be launched in Fall 2009.

HOPA Listserv Service Expansion Proposal: Since the HOPA Listserv (listserv@hoparx.org) was created, its members have used it extensively. Currently, over 5,600 messages are archived on HOPA server. The HOPA membership has asked that listserv messages be archived and accessible online. The Publications Committee is working with DesignWrite to identify the right partner and software to expand HOPA's listserv service.



DRUG UPDATES

Ferumoxytol (Feraheme™)

Class: Novel iron oxide nanoparticle iron replacement

Indication: Treatment of iron deficiency anemia in adult patients with chronic kidney disease

Dose: 510 mg of elemental iron as an intravenous bolus followed by a second 510 mg iron injection 3-8 days later
How supplied: 30 mg/mL as a single-use vial containing 510 mg of elemental iron in 17 ml of isotonic preservative-free mannitol

Dose adjustments: None required

≥2% Adverse Events: Hypotension, hypersensitivity reaction, iron overload, diarrhea, nausea, dizziness, peripheral edema, alteration of magnetic resonance imaging up to 3 months post-dose

Drug interactions: None known

Special instructions: Administer the undiluted intravenous injection at a rate up to 1 mL/sec (30 mg/sec).

Ferumoxytol in Iron Deficiency Anemia

*Susan Woelich, PharmD
 Oncology Pharmacy Practice Resident
 University of Illinois Medical Center*

*Sandra Cuellar, PharmD, BCOP
 Clinical Pharmacist, Oncology
 University of Illinois Medical Center*

Iron deficiency anemia is a common complication of chronic kidney disease (CKD) due to poor iron absorption, chronic blood loss, and increased use of erythropoiesis stimulating agents (ESA), which increases utilization of iron.¹ As a consequence, iron deficiency anemia may reduce the oxygen-carrying load to organs and tissues, resulting in an increased cardiac output.^{2,3} Observational studies indicate that uncontrolled anemia in CKD patients increases left ventricular hypertrophy, impairs quality of life, increases hospitalizations, and increases mortality.^{2,3}

The National Kidney Foundation's (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) recommends a hemoglobin target of 11-12 g/dL.⁴ Erythropoiesis-stimulating agents and iron supplementation are often administered to obtain this target hemoglobin in CKD patients.⁴ Intravenous iron is the treatment of choice due to the limitations

associated with oral iron. Oral iron is convenient, but has low bioavailability and poor tolerability, and patients are typically non-adherent to the prescribed regimen.⁴ Currently, four intravenous iron preparations exist: iron dextran (low and high molecular weight), sodium ferric gluconate, and iron sucrose.¹ Iron dextran has the advantage of allowing a large dose of iron to be given once, but the slow infusion, risk of anaphylaxis, and premedications are unfavorable.¹ Iron sucrose and sodium ferric gluconate have a lower incidence of allergic reactions, but must be administered in small doses due to dose-related side effects.¹

Ferumoxytol is a high molecular weight iron bound tightly to a novel, modified dextran core, resulting in less free iron release into circulation vs other parenteral iron formulations.⁵ The free iron released in circulation is associated with the adverse events reported with the use of other parenteral iron formulations.¹ The formulation of ferumoxytol contains 30 mg/mL of elemental iron in 17 ml of isotonic, preservative-free mannitol.⁶ These characteristics allow ferumoxytol to be given at higher doses as a rapid injection, without a test dose or premedication.⁵ Ferumoxytol is administered in two 510 mg doses, separated by 3-8 days, at a rate of 30 mg/sec.⁵ Due to the higher molecular weight, <1% of ferumoxytol and iron dextran is filtered via dialysis.⁵ Approximately 3% and 5% of total iron is filtered for iron sucrose and ferric gluconate, respectively, and therefore these iron formulations are given at least 1 hour post-dialysis.⁵

Ferumoxytol labeling was approved by the FDA in June 2009 based on safety and efficacy assessed in three randomized, controlled clinical trials.^{1,8-10} In all three controlled trials, a total of 800 subjects were randomized to receive either oral iron or ferumoxytol.^{1,9,10} Two trials included patients with non-dialysis-dependent CKD and the third trial included in patients undergoing dialysis.^{1,9,10} The primary endpoint for these clinical trials was hemoglobin changes and clinical outcomes over a 35-day period.^{1,9,10} Ferumoxytol administration increased the mean blood hemoglobin concentrations by approximately 1.0 g/dL over the 35-day period vs 0.46 g/dL with oral iron (p = 0.0002).^{1,9,10}

In general, ferumoxytol was well tolerated in clinical trials and most adverse effects were seen during or immediately after treatment.¹⁰ The most common reported adverse reactions with ferumoxytol-treated patients vs oral iron included diarrhea (4% vs 8.2%), nausea (3.1% vs 7.5%), dizziness (2.6% vs 1.8%), hypotension (2.5% vs 0.4%), constipation (2.1% vs 5.7%), and peripheral edema (2% vs 3.2%).^{1,9,10} The adverse events that resulted in discontinuation of ferumoxytol included hypotension, infusion site swelling, increased ferritin level, chest pain, diarrhea, and dizziness.^{1,9,10} Serious hypersensitivity

DRUG UPDATES (CONTINUED)

Ferumoxylol continued

reactions occurred in 3 subjects that received ferumoxylol.^{1,9,10} Ferumoxylol may transiently alter the diagnostic ability of magnetic resonance imaging for up to 3 months post-administration.^{1,9,10}

In summary, ferumoxylol is a novel IV iron preparation for iron-deficient anemia in adult patients with CKD.⁷ Ferumoxylol is administered over 17 seconds with a comparable toleration to oral iron.⁷ It may offer advantages over its parenteral formulation predecessors as an alternative iron supplementation with minimal adverse effects and a faster infusion rate. Ferumoxylol is also being investigated as a magnetic resonance imaging contrast agent for malignant brain tumors.¹¹

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Decoding Pharmacogenomic Studies: Basic Definitions

Stacy S. Shord, PharmD, BCOP, Clinical Pharmacology Reviewer, US Food and Drug Administration

Numerous studies indicate that selecting drug therapy based on specific genetic information can improve clinical outcomes by increasing efficacy or tolerability.¹⁻³ The genetic information often describes various metabolic or transport proteins (e.g., cytochrome P450 enzyme or P-glycoprotein) or drug targets (e.g., vitamin K epoxide reductase). Navigating these studies can be difficult without a basic understanding of the terminology and analytical methods. The purpose of this mini-review is to create a legend for these studies and help practitioners better understand studies supporting treatment based on genetic information. Examples of a relationship between genetic variants and clinical outcomes in patients receiving anti-cancer therapies include cytochrome P450 2D6 (CYP2D6) and tamoxifen, uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) and irinotecan, thiopurine methyltransferase (TPMT) and mercaptopurine, and vitamin K epoxide reductase (VKOR) and warfarin. A subsequent mini-review will focus on the genetic information involving the drug targets within the intracellular signaling cascades and the laboratory methods used to measure expression of these various targets, including vascular endothelial growth factor receptor (VEGF) and epidermal growth factor receptor (EGFR).

The terms pharmacogenomics and pharmacogenetics are often used interchangeably and the attempts to distinguish these terms has resulted in multiple definitions for both words. **Pharmacogenetics** is typically defined as the study of inherited differences in an individual or the relationship between a variant in a single gene and clinical outcomes, while **pharmacogenomics** is typically defined as the study of many genes to explain drug outcomes (www.ncbi.nlm.nih.gov). Many clinical trials that incorporate genetic information are focused on the variation in the genes that encode drug metabolism or transport proteins with the goal of improving patient tolerability.

A **genome** is the genetic information of an organism (such as a human); this information is encoded by DNA. A linear strand of DNA and associated proteins make up a **chromosome**. An individual inherits 23 chromosomes from each parent, so the nucleus of each cell contains a total of 46 chromosomes. Each gene in an individual is represented by two copies called alleles (one on each chromosome). An **allele** is therefore defined as a series of genes that occupy a specific position on a chromosome. This pair of alleles may be the same (**homozygous**) or different



DRUG UPDATES (CONTINUED)**Decoding Pharmacogenomic Studies: Basic Definitions** continued

(**heterozygous**). A **haplotype** is a groups of alleles located on different **loci** (defined as a specific site on a chromosome) on the same chromosome that are inherited together. The most common version of a gene is referred to as the **wild-type** allele. **Mutations** are rare DNA changes that are not repaired (occur in less than one percent). In contrast, **polymorphisms** are DNA changes that are common. Mutations and polymorphisms may be introduced and carried to the next generation.

The most common polymorphism is a single-base substitution or single nucleotide polymorphism (SNP [pronounced as “snips”]). A purine (adenine or guanine) may be substituted for a pyrimidine (cytosine or thymidine) (or vice versa, labeled as a **transversion**) or another purine (labeled as a **transition**). A polymorphism is characterized as a **missense** mutation if the substitution yields an altered amino acid or **nonsense** mutation if the substitution yields a stop codon and truncates the amino acid sequence. A missense mutation may also be referred to as a **non-synonymous** SNP. A **silent** mutation or **synonymous** SNP occurs when a single-base substitution does not produce a change in the amino acid sequence. A silent mutation can occur because more than one **codon** (defined as three adjacent nucleotides) encodes each amino acid.

Other mutations that can occur include splice site mutations, insertions and deletions, and copy number variants. Splice sites are located between **introns** (non-coding DNA) and **exons** (coding DNA) and tell the cellular machinery what DNA to excise before translating the DNA to messenger RNA. **Splice site mutations** occur when the introns are translated to mRNA. Insertions and deletions occur when one or more nucleotides are added or removed from the DNA and may be referred to as **indels**. The indels often cause **frameshift** mutations, such that the reading frame is altered and leads to a different amino acid sequence. Indels may also inadvertently produce a stop codon following a frameshift mutation and truncate the amino acid sequence. The transcribed protein may possess increased or decreased activity or may be non-functional (**null allele**). **Copy number variants** occur when more than two copies of an allele can occur. For example, 13 alleles of *CYP2D6* were identified in a brother-sister pair.⁴

The consequences of these variations depend on two factors. The first factor is the number of copies of the variant allele. Heterozygotes typically experience less alterations in protein function compared to homozygotes for the variant allele (if the alleles are co-dominant).⁵ Assuming that a homozygote for the wild-type allele possesses 100% of metabolic capacity,

a heterozygote would possess 75% of the metabolic capacity of a homozygous wild-type and a homozygote variant allele would possess 50% of the metabolic capacity, if each variant allele demonstrated a 25% reduction in metabolic capacity. A homozygote wild-type and heterozygote are commonly labeled **extensive metabolizers**, whereas a homozygote variant is commonly labeled a **poor metabolizer**. For some genes, such as *CYP2D6*, a heterozygote is labeled as an **intermediate metabolizer**. Individuals with a duplication of a functional allele typically display metabolic capacity greater than a homozygote for the wild-type allele and are labeled as an **ultrarapid metabolizer**.

The second factor is the location of the variation. The variation may be located in an intron, an exon or a regulatory region. Variations located in an exon or regulatory region are more likely to influence translation and transcription. Each protein contains both a ligand-binding domain and at least one transmembrane domain. If the substitution is located in the ligand-binding domain, the drug will likely interact differently with the protein. Moreover, the interaction of the altered protein will be different for each drug.⁵ Therefore, the percentage change in the amount of drug transported or metabolized will be different for each drug. As an example, one of the more common variant alleles identified for *CYP2D6* is the reduced function *17 allele. This polymorphism is associated with reduced hepatic or systemic clearance of the probe drug dextromethorphan⁶; however, it is not clear if this polymorphism is associated with reduced metabolism of other *CYP2D6* substrates, such as tamoxifen and metoprolol. Furthermore, the functional consequences of the variation may differ by race. It appears the dextromethorphan to dextrophan metabolic ratio commonly used to measure *CYP2D6* activity demonstrates a “right-shift” in Blacks, suggesting that the definitions of metabolic status defined for Caucasians may not apply to Blacks and other races.⁶

For genetic variations that affect drug metabolism, the clinical consequence will depend on the relationship between the pharmacokinetic properties and clinical outcomes. Differences are more likely to be noted for drugs with narrow therapeutic windows, such as warfarin, than other drugs in which a wide plasma concentration range is tolerated and associated with therapeutic outcomes (e.g., antihypertensives). For example, the *UGT1A1**28 allele contains an insertion labeled a **tandem repeat**, defined as two or more nucleotides that repeat and the repetitions are directly adjacent to one another. The altered sequence leads to reduced metabolism of the glucuronidated SN-38 metabolite of irinotecan following an intravenous infusion.

DRUG UPDATES (CONTINUED)

Decoding Pharmacogenomic Studies: Basic Definitions *continued*

The systemic exposure to SN-38 increases in heterozygotes and homozygotes for the *28 allele, and the individuals may experience more myelosuppression and diarrhea.⁷ It appears that personalized medicine is more likely to be incorporated into clinical practice for drugs, such as irinotecan, with a narrow therapeutic index, since the pharmacokinetic properties of these drugs is correlated to clinical outcomes.

At this point in time, personalized medicine is not common practice despite evidence that a relationship exists between clinical outcomes for specific drugs and identified polymorphisms for various metabolic and target proteins. However, the PI for some drugs, including tamoxifen, irinotecan, mercaptopurine, and warfarin, contains information regarding genetic testing. Limitations to genetic testing include ethnic differences, cost, and availability. Ethnic differences in the frequency of a polymorphism are apparent for many metabolic and target proteins, which makes broad recommendations across racial and ethnic groups difficult to justify. For example, the *CYP2D6*17* allele is very common in Blacks, but seldom identified in other races. The analytical methods needed to perform genetic tests are not available in many medical centers, and blood samples must be sent to an outside laboratory for DNA analysis. The last barrier is cost; not all insurance providers pay for the testing and it is not known if the cost of the testing will improve efficacy and tolerability and reduce related health care costs, such as hospitalizations and supportive care related to poor response or serious adverse events.

Studies incorporating genetic information may focus on a single variant (referred to as the candidate gene) or the genome with the objective of finding an association between a variant or group of variants and clinical outcomes, such as incidence of a disease or adverse events. Genome-wide studies may be labeled as “fishing expeditions” and the results may be restricted by rare variants, alleles with small effect sizes, population differences (e.g., ethnic and racial), epistatic interactions (synergy vs. antagonism), epigenetic differences, copy number variants, and disease heterogeneity. Candidate gene studies are limited by the *a priori* assumptions, such as the relationship between the gene and the pharmacokinetic property or clinical outcome, which may lead to a false-positive result. Other limitations associated with these study designs include common statistical errors associated with multiple variables, small populations, etc.

It is also important to have a basic understanding of the more common laboratory tests incorporated into these studies. DNA is typically isolated from whole blood or epithelial cells of the

oral mucosa. The DNA sequence containing the allele is then amplified using polymerase chain reactions (PCR). PCR requires the use of two DNA sequences that are complementary to the DNA sequence of interest, a forward and reverse primer. Various laboratory techniques are then used to identify variant alleles, including restriction fragment length polymorphism (RFLP) or sequencing. RFLP uses restriction enzymes to cut the DNA in multiple places. The fragments are then separated on a gel and the fragment sizes examined. The fragment sizes are different for the wild-type and variant alleles. DNA sequencing is more commonly used to identify variant alleles and multiple methods are available to sequence the DNA. Two common methods use fluorogenic probes or binding dyes to identify the variant allele in the amplified PCR product. Other methods include pyrosequencing and capillary electrophoresis. These methods identify the variant allele using a technique sometimes called “sequence by synthesis,” and the DNA sequence can then be compared to the wild-type allele to identify the absence or presence of a variant allele. Multiple variant alleles may be detected using microarray platforms (such as AmpliChip™, Roche Diagnostics) that incorporate some of the methods described herein for the detection of one variant allele. All of these methods are commonly used to identify variant alleles which the selection based on many factors, such as time, cost, and availability.

In summary, genetic information and testing is becoming an integral part of anti-cancer therapy and supportive care for patients with cancer. The literature regarding the identification and the potential impact of these polymorphisms is quickly expanding and could ultimately change our current clinical practices. However, to review the literature requires a basic understanding of the different polymorphisms and the laboratory techniques. In this mini-review, the foundation for further review of the primary literature regarding polymorphisms in drug metabolism and transport was discussed.

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