What We Carried on Christmas
Fiction for the Year’s Best in Hematology

JASON GOTTUB, MD, MS, Editor-in-Chief

Editor’s Note: The characters in the following story are fictionalized versions of patients we have managed on the hematology service. The title “What We Carried on Christmas” is a tribute to “The Things They Carried,” Tim O’Brien’s critically acclaimed short story from 1987 that uses the list as a writing form to tell a powerful story of a platoon in Vietnam. The commentary following this piece provides my perspective on how hematology advances, including 2015 Year’s Best selections, weave together with the compelling narratives of our patients’ lives.

My Christmas morning commute to Stanford Hospital felt like a post-apocalyptic odyssey. I didn’t spot a single car or human being on the eight-mile stretch of Interstate 280. However, shortly after taking the off-ramp to Sand Hill Road, I came upon a freshly struck deer lying in the left lane. I slowed down and surveyed the carnage. Its warm entrails formed an accidental palette with the shoulder’s yellow border. Along this corridor of venture capital firms, a Tesla sped off from the scene. It carried dollops of the deer on its front grille, while leaving an electric hum in its wake. The driver joked about the similar textures and tastes of combat MREs and our cafeteria’s in Mogadishu and Operation Enduring Freedom against the Taliban. During treatment, his waning appetite made him snatching a high-value target.

On Christmas morning, Paul carried an extra 5 kg of fluid from his AML induction. The edema made little difference on the 6’6”, 120-kg frame that he sculpted during Army Special Forces training in the early 1990s. His physique blended a perfect combination of slow-twitch and fast-twitch muscle memory that made it easy to double-tap a target while hanging upside down in the dark. Paul carried the tip of the spear as a member of Delta Force during two Gulf wars and numerous clandestine ops around the globe. The team stared at his massive figure when he hopped around the hematology unit with his diminutive IV pole; the nurses and other patients gawked, too, like rubberneckers transfixed by that strok-edge of a deer. When United Airlines Flight 77 tore into the Pentagone, Paul had scooped up workers and carried them to safety before the ceiling of their office collapsed. For a few hours, he inhaled a plume of super-heated dust consisting of incinerated concrete, fuselage, and parts of people’s souls. His lungs carry the scars of that day. A few months after 9/11, he developed pneumonitis and lost a quarter of his pulmonary function. It’s possible the toxic brew also corrupted his bone marrow.

During morning rounds, Paul shared tidbits from some of his Delta Force missions, including Operation Gothic Serpent in Mogadishu and Operation Enduring Freedom against the Taliban. During treatment, his waning appetite made him think of meals at home and abroad. He joked about the similar textures and tastes of combat MREs and our cafeteria’s selections. He remembered about toppings that presaged the dinner menu at his base in Kabul: horseradish on the tables in two weeks, he’ll leave the hospital. When I have the results of his remission marrow, he’ll be

Paul’s three children and wife spent Christmas day with him in his room. He hopes that his illness will bring them closer together. In two weeks, he’ll leave the hospital. When I have the results of his remission marrow, he’ll be

(Cont. on page 6)
A New Year Full of Promise for ASH

As we enter into the New Year, I would like to acknowledge the support and leadership that Dr. David Williams has provided ASH and its members throughout 2015.

In the past several years, the January/February issue of The Hematologist has looked back at the previous year’s accomplishments and has celebrated the way in which ASH’s annual meeting conveys the breadth and depth of the discipline. This year in Orlando, I was impressed with the rapid rate of progress and discovery that the field of hematology is currently enjoying and the unique and enticing opportunities where ASH could play a leading role.

Some of the most meaningful ways ASH can lead is by steadily growing, and refining, the Society’s content offerings. With each issue of Blood, there continues to be a drive toward high-quality, cutting-edge research, resulting in novel therapies across a wide variety of subspecialties. Additionally, in 2016, these efforts will continue with the launch of a new journal from ASH, designed to keep both researchers and clinicians abreast of topics in emerging areas, including, but not exclusive to, immunotherapies and gene editing.

In addition to publications, ASH will launch new educational offerings in 2016 that are in line with the explosive breakthroughs in hematology. To shed continued light on the latest advances in basic and translational lymphoma research, the second Meeting on Lymphoma Biology will take place in June in Colorado Springs, Colorado, while the second ASH Meeting on Hematologic Malignancies in September will feature clinical breakthroughs and cutting-edge treatment approaches to lymphomas, leukemias, and other malignant conditions. Furthermore, because training is so pivotal to our ongoing progress and mission, ASH will launch the Medical Educator’s Institute, which will equip medical educators with a “boot camp” that will cover teaching techniques, as well as proper evaluation of trainees and programs.

It is impossible to discuss the influx of innovation without also mentioning new drugs and precision medicine. At the 2015 Annual Meeting, there were three developers in partnership with the U.S. Food and Drug Administration devoted to the recent introduction of exciting new drugs available in benign and malignant hematology. With regard to precision medicine, ASH’s newly defined Agenda for Hematologic Research has prioritized the areas of genomic profiling and clinical biology and has also created a task force on precision medicine to identify and capitalize on the opportunities in hematology. Building on the research that has been conducted by our members, 2016 is gearing up to be an exciting year in which developments in new drugs and novel treatments based on the human genome will continue on the path to becoming clinically meaningful.

Impressive momentum abounded all throughout hematology last year, and sickle cell disease (SCD) was no exception. From promising improvements in gene therapy, to new approaches for vaso-occlusion, SCD researchers saw some incredible advancements. To strengthen the pace of innovation, ASH announced a new “Call to Action” for SCD during an April 2015 Summit, and in 2016, the Society will expand on the strategies identified, to create new work groups focused on access to care, research, and global outreach.

Finally, 2016 will be another year in which ASH continues to expand outreach and growth on a global scale. To begin with, we were excited to announce, after the close of the 2015 annual meeting, a newly approved category of membership that gives international members the right to vote, and that gives the Nominating Committee the flexibility to nominate international candidates to run for a Councillor position, as appropriate for the needs of the Society, at any given time.

Another bylaws amendment has created a membership category for International Associate members, which allows trainees outside of North America to join and enjoy a member benefits package similar to that of Associate members in North America.

I am incredibly proud to help realize the promise of the new year as president of ASH, as our Society continues to demonstrate its leadership in some of the most thrilling areas of scientific and clinical exploration.

Bernard G. Forget, MD (1939-2015)

Dr. Bernard G. Forget died on November 6, 2015, at the age of 76, after a three-year battle with cancer. The hematology community has lost one of its most beloved and esteemed colleagues.

Bernie was born in Fall River, Massachusetts, where his French Canadian father served as a dedicated general practitioner. After undergraduate training at the University of Montreal, Bernie received an MD in 1963 from McGill University where he was class valedictorian. Following a residency and fellowship at Massachusetts General Hospital, he received training in hematology at the National Institutes of Health (NIH) and at Children’s Hospital in Boston. His early scientific development was fostered by the mentoring of Drs. Roger Monier, Sherman Weissman, and David Nathan.

In 1976, Bernie joined the Departments of Medicine and Human Genetics at Yale University where he devoted the remainder of his career. He was chief of Yale’s Section of Hematology from 1976 to 1987, and again from 1993 to 2005. During this 30-year span, he made landmark research contributions and have laid the groundwork for a generation of students, residents, and fellows, many of whom have become leaders in hematology research and clinical practice.

Bernie and his research team pioneered studies of molecular pathogenesis of congenital red cell disorders. He was the first to use specific ribonucleases to prepare two-dimensional maps of globin mRNA that enabled sequence information to be generated on both coding and noncoding segments. This early work was critically important in facilitating the cloning of globin genes. His studies of the flanking regions of the human \( z \)-genes provided insight into the physiologically and clinically important switch from \( y \)- to \( f \)-gene expression. Subsequently, Bernie’s lab focused on the molecular genetics of red blood cell (RBC) membrane proteins. His lab was the first to clone and sequence genes encoding \( z \)- and \( f \)-spectrin, the major proteins of the RBC cytoskeleton. These studies paved the way toward a molecular understanding of the assembly of red cell membrane proteins. Bernie’s work on the globin genes and on those encoding RBC membranes have clear-cut relevance to important blood disorders such as thalassemia, sickle cell disease, and congenital hemolytic anemias due to mutations in red cell membrane proteins.

During his long and remarkably productive career, Bernie received many honors, including membership in the American Society for Clinical Investigation, the Association of American Physicians, and the American Academy of Arts and Sciences. He was awarded the Henry M. Stratton Medal from ASH in 1996 and was the recipient of the Yale Cancer Center Lifetime Achievement Award in 2013.

A happy and fulfilling family life was a huge contributor to Bernie’s remarkable record of leadership and discovery. During their time together at the Yale-New Haven Hospital, she and Bernie were blessed with three children and three grandchildren. The Forget family cherished time together at their seaside home in Rhode Island as well as frequent trips to France, which helped sustain Bernie’s Gallic pride and temperament.

—H. Franklin Burns, MD, Hematology Division, Brigham and Women’s Hospital, Harvard Medical School
The Hematologist: ASH Meeting on Lymphoma Biology will take place June 18-21 at The Broadmoor in Colorado Springs, Colorado. This meeting will bring together experts from around the world to discuss the latest breakthroughs in basic and translational lymphoma research, address current challenges in the field, and help promote efforts to accelerate the development of new therapeutic strategies. The event spans four days and features didactic sessions, abstract presentaions, interactive workshops, and panel discussions. For registration fees, speaker information, and more, please visit www.hematology.org/malignancies.

Learn More about the New ASH Medical Educators Institute

This new program provides hematologists who are new to medical education with a “boot camp” for teaching techniques, medical education scholarship, and trainee and program evaluation. Topics that will be discussed include educational research design in hematology, use of technology in medical education, adding value to your institution as a hematology educator, small group instruction, and the ins and outs of promotion and tenure. ASH will subsidize participation in the program by covering costs of travel, lodging, and meals. For additional information, visit www.hematology.org/educators/4692.aspx.

Register for the First-Ever ASH Workshop on Genome Editing

The ASH Workshop on Genome Editing will take place July 14-15, 2016, at the Omni Shoreham Hotel in Washington, DC. This workshop was created to provide a forum that focuses on the mechanistic aspects, and possible clinical implications of genome editing for blood disorders. Academic researchers, industry scientists, regulators involved in the clinical application of the technology, and other interested individuals are encouraged to attend. Learn about the basic science of genome editing, its application in clinical, current scientific challenges in using this tool for research purposes, application of the technology to hematologic disorders, as well as regulatory issues. There will also be ample opportunities to network with colleagues and world-class experts, and to explore possible collaborations. For a list of speakers and additional information, and to register online, visit www.hematology.org/genome-editing.

The Hematologist Board of Contributing Editors Maintains the Cycle of Excellence in 2016

The yearly convening of The Hematologist Editorial Board at the ASH annual meeting always marks a time of transition. In December 2015 in Orlando, we expressed our gratitude to four outgoing Contributing Editors: Drs. Mark Koury, Peter Johnson, Pamela Becker, and Charles Quinn. Both Drs. Koury and Johnson served for consecutive terms.

Since first joining the editorial board in 2012, Mark, with his wealth of expertise in erythropoiesis along with 30 years of experience in research and clinical practice at Vanderbilt University, has endowed this publication with dozens of challenging, thought-provoking contributions. We will greatly miss the enthusiasm of Southampton General Hospital’s Peter Johnson, whose thoughtful Diffusion selections brought us the most significant developments in topics from lymphoma, to molecular diagnostics, to emerging antibody therapeutics. We also had the benefit of working with Pamela Becker of the University of Washington. Pam’s incredible expertise in a wide range of areas across malignant and nonmalignant hematology, particularly in acute myeloid leukemia and stem cell and regenerative medicine, filled a great need and served our readership well. Finally, we owe a great debt to Charles Quinn of Cincinnati Children’s Hospital Medical Center. With his deep knowledge of sickle cell disease and thalassemia, Charles provided ASH and its members with precise and steadfast coverage of these increasingly vital topics.

Four new contributing editors have been appointed to fill the vacancies left by the departures of Drs. Koury, Johnson, Becker, and Quinn.

Dr. Omar Abdel-Wahab is an assistant attending physician on the leukemia service at Memorial Sloan-Kettering Cancer Center and a member of the Human Oncology and Pathogenesis Program. His laboratory is focused on the fundamental understanding of genetic alterations in patients with chronic myeloid and lymphoid leukemias. One of his main areas of interest is in understanding the biological and therapeutic significance of epigenetic and transcriptional alterations in patients with leukemia. He also serves on the editorial board of Blood.

Dr. Michael DeBaun is professor of pediatrics and medicine, JC Peterson Endowed Chair in Pediatrics, vice chair of clinical and translational research in pediatrics, and the founder and director of the Vanderbilt-Meharry Center for Excellence in Sickle Cell Disease at Vanderbilt University School of Medicine. He is an internationally recognized physician-scientist whose research has resulted in fundamental advances in the genetics of cancer predisposition syndromes and the epidemiology and optimal treatments of stroke and lung disease in sickle cell disease. Dr. DeBaun has mentored numerous medical and graduate students and postdoctoral fellows, several of whom have gone on to receive multiple investigator-initiated federal grants and foundation awards. Dr. DeBaun is an elected member of the American Society for Clinical Investigation, the Association of American Physicians, the Institute of Medicine of the National Academy of Sciences, and the American Association for the Advancement of Science. In 2014 he was honored by ASH with the Ernest Beutler Lecture and Prize in Clinical Science.

Dr. Paul Moss is professor of hematology and director of medical research at the University of Birmingham, UK. He is also chair of the Infections & Immunity Board at the Medical Research Council, and previously served as Chair of the Cancer Research UK Clinical and Translational Research Committee. Professor Moss has a clinical interest in lymphoproliferative and immunological disorders. His research program focuses on translational immunity within cancer, transplant, and viral disorders. He is author of Essential Haematology, one of the most popular international textbooks on hematology.

Dr. Sioban Keel is a clinician-scientist at the University of Washington in Seattle. Her research centers on defining the phenotypic spectrum and genetic and molecular mechanisms regulating hematopoiesis and marrow failure in inherited bone marrow failure syndromes and inherited predisposition to leukemia and myelodysplastic syndromes. She brings research expertise in the molecular and cellular events that control red blood cell development, which synergizes with her active clinical practice. Dr. Keel cares for adult patients with inherited and acquired marrow failure, intrinsic red blood cell disorders, and unexplained cytopenias at the Seattle Cancer Care Alliance, and both directs and attends on the inpatient hematology consult service at the University of Washington.

We look forward to having Omar, Michael, Paul, and Sioban lend their unique viewpoints regarding the molecular underpinnings of leukemia, hemoglobinopathies, immunotherapeutics, and marrow failure states, respectively. The benchtop, clinical, and translational interests of The Hematologist Board of Contributing Editors mirror the education, research, and patient care missions of ASH – malignant and non-malignant hematology, pediatric disease, genomic/precision medicine, stem cell biology, hematopathology, and global health. Through our popular Diffusion articles, Ask the Hematologist, and Mini Review pieces, as well as multimedia platforms such as podcasts, our goal is share the dynamic developments in our field while speaking to the broad demographics of our Society. We are always interested in readers’ ideas so that our content can best serve the voices and passions of ASH’s membership.

Follow Blood on Twitter!

Stay up to date with Blood, the official journal of ASH, and the most cited peer-reviewed publication in the field of hematology. Follow the journal on Twitter through the handle @Bloodjournal.

Save the Date for the 2016 International Highlights of ASH

Highlights of ASH provides a summary of the top hematology research presented at the 57th annual meeting in Orlando, to help improve patient management and care strategies. Look out for this year’s International Highlights of ASH:

- Latin America: April 29-30 – Natal, Brazil
- Asia-Pacific: March 5-6 – Brisbane, Australia

For more information, visit www.hematology.org/highlights.
by Dr. Andrew Zelenetz demonstrated what happens when an inhibitor of the PI3 Kinase pathway, idelalisib, is added to bendamustine and rituximab (BR). In a randomized, double-blind, placebo-controlled phase III study, the three-drug combination showed an impressive improvement in progression-free and overall survival over BR alone. In that same session, Dr. Stephen Stilgenbauer presented results from a phase II study, which used a BCL-2 inhibitor (venetoclax; ABT-199), in patients with del(17p) relapsed or refractory CLL, also with impressive results in this notoriously challenging subset.

Multiple myeloma (MM), which was long known as a specialty of therapeutic nihilism, has become a poster child for rapid translation of molecular discoveries into the clinic. In 2015, the FDA approved four agents for the disease, panobinostat, ixazomib, daratumumab, and elotuzumab, each of which takes advantage of a different mechanistic vulnerability of the myeloma cell. At this year’s meeting, attendees were presented with numerous new studies that incorporated these agents either alone or in combination with established therapies. For example, Dr. Saad Usmani presented combined results of two studies that treated a total of 1,483 patients with late-stage MM with daratumumab and dexamethasone. In the double-blind, placebo-controlled phase III study, which took advantage of a different mechanistic vulnerability of the spliceosome, such progress bodes well for future therapies.

Targeted therapy is beginning to reach the myeloid world as well. Long held out as “too heterogeneous” for a targeted approach, the last two ASH annual meetings have demonstrated the important role that inhibitors of the constitutively activated FLT3 receptor play in the treatment of acute myeloid leukemia (AML). During the Plenary Scientific Session, Dr. Richard Stone revealed the important findings of the RATIFY study, a CALGB/Alliance effort that took years of work in accrual and logistical management. This study randomly assigned patients (ages 18 to 60 years) with newly diagnosed, FLT3-mutated (ITD or TKD) AML to 7+3 alone or in conjunction with the FLT3/multikinase inhibitor, midostaurin. The study showed that addition of midostaurin improved the event-free and overall survival of patients (whether censored or uncensored for transplantation), with this genetically defined subgroup of AML. These data pave the way for drug approval, and may herald an end to the four-decade period of relative therapeutic nihilism, has become a poster child for rapid translation of molecular discoveries into the clinic. In 2015, the FDA approved four agents for the disease, panobinostat, ixazomib, daratumumab, and elotuzumab, each of which takes advantage of a different mechanistic vulnerability of the myeloma cell. At this year’s meeting, attendees were presented with numerous new studies that incorporated these agents either alone or in combination with established therapies. For example, Dr. Saad Usmani presented combined results of two studies that treated a total of 1,483 patients with late-stage MM with daratumumab and dexamethasone. In the double-blind, placebo-controlled phase III study, which took advantage of a different mechanistic vulnerability of the spliceosome, such progress bodes well for future therapies.

Targeted therapy is beginning to reach the myeloid world as well. Long held out as “too heterogeneous” for a targeted approach, the last two ASH annual meetings have demonstrated the important role that inhibitors of the constitutively activated FLT3 receptor play in the treatment of acute myeloid leukemia (AML). During the Plenary Scientific Session, Dr. Richard Stone revealed the important findings of the RATIFY study, a CALGB/Alliance effort that took years of work in accrual and logistical management. This study randomly assigned patients (ages 18 to 60 years) with newly diagnosed, FLT3-mutated (ITD or TKD) AML to 7+3 alone or in conjunction with the FLT3/multikinase inhibitor, midostaurin. The study showed that addition of midostaurin improved the event-free and overall survival of patients (whether censored or uncensored for transplantation), with this genetically defined subgroup of AML. These data pave the way for drug approval, and may herald an end to the four-decade period of relative stagnation in the field of AML therapeutics.

The momentum is not limited to areas of malignant disease. Since the discovery of thrombopoietin (TPO) more than 20 years ago, numerous biologic insights have been made regarding its interaction with its receptor c-mpl. This signaling pathway’s role in megakaryocyte production and regulation of platelet mass has been therapeutically exploited, leading to drug approvals of the TPO mimetics romiplostim and eltrombopag in patients with idiopathic thrombocytopenic purpura. TPO also has an established role in regulating hematopoietic stem cells, which led Dr. Cynthia Dunbar, Neal Young of the National Institutes of Health (NIH) to first determine whether one can safely modulate LRF’s usual suppression of fetal hemoglobin to mitigate the clinical consequences of sickle cell disease. Similarly, the first in vivo evidence on how to modulate the spliceosome in myeloid malignancies was presented by Dr. Stanley Chun-Wei Lee on behalf of the laboratory of Dr. Omar Abdel-Wahab at Memorial Sloan Kettering Cancer Center. Recognizing the challenges of keeping up with changes in the diseases we treat, in the last several years ASH has added several additional in-depth sessions that cut across diseases. This year, there were two well-attended Friday scientific workshops: one on myeloid diseases and the other on hematology and aging. On Saturday, there was a special interest session on newly approved drugs, shedding light on the right time and place to utilize drugs like blinotumumab, panobinostat, and danusitrumab. Attendees even had an hour-long educational session on social media and Twitter, and the many ways these ubiquitous technologies might be productively used by physicians and patients.
ASH Continues Advocacy to Ensure Patient Access to Safe and Effective Hematologic Drugs

While oral and patient self-administered forms of chemotherapy have become more prevalent, and represent the standard of care for many types of cancers, they are covered differently than intravenous drugs, leaving many patients responsible for unsustainable, high monthly co-payments.

As part of the Patients Equal Access Coalition (PEAC), ASH has advocated for legislation in the U.S. House of Representatives and the U.S. Senate (H.R. 2739/S. 1566, the Cancer Drug Coverage Parity Act) to ensure that cancer patients have equality of access (and equality of insurance coverage) to all approved anticancer regimens including, but not limited to, oral and intravenous drugs. Several ASH committees, as well as members of the ASH Advocacy Leadership Institute, advocated for the legislation throughout 2015 and secured the support of a number of members of Congress. The sponsors of the legislation in both the House and Senate remain committed to the issue and are working to urge committees in both houses to hold hearings, with the ultimate goal of passing the bills before the conclusion of the 114th Congress in December 2016. Visit the ASH Advocacy Center at www.hematology.org/TakeAction to send an email to your Senators and Representative urging them to support the Cancer Drug Coverage Parity Act.

Although only federal legislation will ensure coverage for all cancer patients, 40 states plus the District of Columbia have passed legislation to limit patient out-of-pocket costs for oral anticancer medications. ASH has supported legislative efforts at the state level as well, and will continue to work with stakeholders and advocacy groups to support ongoing legislative efforts in a number of additional states in 2016, including Michigan, Tennessee, Alabama, North Carolina, and Pennsylvania. If you live in one of these states and are interested in working with ASH to help ensure your patients have affordable access to oral chemotherapy drugs, please contact ASH Legislative Advocacy Manager Tracy Roades at troades@hematology.org.

ASH Submits Comments in Response to Proposed Rulemaking on the “Common Rule”

The Obama Administration released a Notice of Proposed Rulemaking (NPRM) to modernize, and strengthen the Federal Policy for the Protection of Human Subjects, otherwise known as the “Common Rule.” By way of background, in 2011, the Obama administration published an Advance Notice of Proposed Rulemaking (ANPRM), “Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators,” to seek more information on how the Common Rule might be improved and revised to be more effective. The current NPRM proposal, which was published in the Federal Register on September 8, 2015, incorporates the feedback received from the ANPRM. The proposed rule is designed to streamline the federal oversight of human subjects protections while reducing administrative burden, delay, and confusion for researchers. Once promulgated, the regulations would impact every research discipline funded by every federal agency, as well as clinical trials, regardless of funding source.

One of the most fundamental changes in the Common Rule as proposed in the NPRM is the inclusion of biospecimens in the definition of human subjects research. The focus of the NPRM is to require informed consent for research involving biospecimens in all but a limited number of circumstances. The consent would not need to be obtained for each specific study using the biospecimen, but instead would be obtained through broad consent for future unspecified research.

ASH solicited feedback on the NPRM from the ASH Committee on Government Affairs and the Committee on Scientific Affairs, and submitted final comments to the government on January 6, 2016. The Society's complete comments may be found on the ASH website at www.hematology.org/Advocacy/Testimony. At the time of publication, it is unclear when a final rule will be published.
What We Carried on Christmas

(Cont. from page 1)

studiying my face for clues about good or bad news. Reading microexpressions is part of his training. Paul carries the unflinching faith that he’ll dodge another bullet. He visualizes a military retirement, lounging at his beachside home, out from the shadows and cured of AML. In this future, he’ll make the choice to sport a buzz cut, despite it occasionally reminding him of the time when nurses carried away clumps of his hair.

Olivia is a 32-year-old blonde with television good looks who came in carrying a new quilt of bruises. She and her husband, owner of a private equity firm, live in an 8,000-square-foot home in Atherton. They are warm and soft-spoken. Their two girls, ages three and six, are angelic clones of their mother. Photos of the kids and their crayon drawings blanket the walls of her hospital room. When the resident and first-year fellow first spied her D-dimer of 20,000 mg/mL, fibrinogen of 42 mg/dL, platelet count of 19 × 10^9/L, and white blood cell count of 77 × 10^9/L, they understandably carried apprehension and urgency. I felt the same. They heard of the head bleeds; I managed them; our APL patients died of them. We started ATRA and successfully FISHed for t(15;17).

Olivia steadied her shaky voice; she carried guilt, fear, and many questions about things she was afraid to ask since she first heard the word “leukemia.”


She inspected her bruises. She was unconflicted that she wasn’t to blame. Tears welled in her eyes.

“Am I going to give this to my kids?” she asked.

“No. None of this is your fault. This is an acquired blood cancer. You can’t pass this on to your children,” I comforted her.

We commenced a protocol for high-risk APL and reassured her that she has an excellent chance of being cured. However, we all knew that she wasn’t out of the woods.

A year ago, I lost a mother of three young kids to relapsed acute lymphoblastic leukemia. Soon after, her husband reconnected with me. While he was thankful and trying to move on, Olivia’s case reminded me that I hadn’t! I still carried an insidious melancholy that bubbled to the surface: It hung on to my conscience the way dried silicone gel sticks to jeans despite repeated washings.

I felt that this was a good time for bargaining. I rationalized that if all creatures are equal in God’s eyes, maybe he would agree to a zero-sum arrangement: Olivia for the deer. I turned to her husband to make sure there would be no last-minute hiccup.

“Do you drive a Tesla?”

Commentary: Our patients remind us daily of what we are fighting for. While there may be “eight million stories in the naked city,” we are privileged to be witnesses to a few thousand of them during our careers. In some cases, we can extend patients’ quantity and quality of life so that new epilogues and second chances can be written.

2015’s Year’s Best in Hematology is a subjective list that highlights the achievements of our profession. Our choices mark time and allow different arcs of progress to reveal themselves. However, these choices are most relatable and personal when we can identify specific patients who are beneficiaries of these breakthroughs. Olivia’s promising outlook reflects a narrative of incremental progress in APL throughout the past 30 years. I remain hopeful for Paul. Genomic studies are helping to inform drugable pathways for different subsets of patients with AML. Separately, a day before Christmas, a man with a white blood cell count greater than 100 × 10^9/L walked into our emergency department. He left a day later with a diagnosis of chronic phase CML, a TKI prescription, and unexpected hope.

The transformative success of CML therapy could not have been fleshed out nor appreciated in a single Year’s Best article. I am curious to see how studies of clonal hematopoiesis, myeloma antibodies/immunotherapy, techniques to enhance stem cell engraftment, and the other Year’s Best selections featured herein pay dividends for our patients over the long haul. I will let you know when I am on service again during Christmas 2025.

From Jules Dassin’s “The Naked City”

READER SURVEY

RANKINGS FROM THE HEMATOLOGIST

This ranking reflects the results of a survey in which readers of The Hematologist scored several topics from “most influential” to “least influential.” The following articles reflect the top choices of the Editor-in-Chief and individual Contributing Editors.

1) Anti-CD19 CAR T-cells for refractory DLBCL
2) Antibodies and immunotherapy for multiple myeloma
3) Reversal agents for direct oral anticoagulants
4) Age-related clonal hematopoiesis in normal individuals
5) Reprogramming of Ph+ ALL cells into nonleukemic macrophages
6) PET-directed therapy for early Hodgkin lymphoma
7) Novel mechanisms of regulation of blood production
8) Boosting hematopoietic stem cell engraftment
9) Perioperative bridging anticoagulation and atrial fibrillation
10) Mutation order and myeloproliferative neoplasms
11) Biologic insights into malaria infection and resistance
12) Practice-defining trials: fresher blood and IVC filters
13) New therapeutic frontiers in sickle cell disease
14) Optimizing maintenance therapy in ALL
15) Somatic mutations in aplastic anemia
The topic of age-related clonal hematopoiesis is a compelling story in late 2014 and dominated 2015 as a subject hematologists are still grappling to understand. It has become clear that in some individuals, these somatic clones might not always remain quiescent or harmless. Instead, they may contribute to clonal expansion and overt development of myeloid neoplasms with the acquisition of additional cooperating mutations.

One year ago, in the January/February 2015 Year’s Best Issue of the Hematologist, Dr. Ravi Majeti authored the article titled “Pre-Leukemic Hematopoietic Stem Cells in Human Acute Myeloid Leukemia.” He highlighted the seminal findings, published concurrently by three groups,1-3 that some of the typical recurrent mutations found in acute myeloid leukemia (AML) could also be found in the peripheral blood of patients without a prior diagnosis of hematologic disease. Dr. Majeti raised the question of whether these individuals could be followed with the goal of detecting overt disease earlier, allowing for early treatment and/or prevention.

The studies by Dr. Siddhartha Jaiswal,1 Dr. Giulio Genovese,2 and Dr. Mingchao Xie3 and their respective colleagues established that these acquired mutations occurred with normal aging and were akin to precursor conditions such as monoclonal gammopathy of undetermined significance (MGUS) or monoclonal B-cell lymphocytosis (MBL). Analysis of mutations in 12,380 individuals in a Swedish study4 revealed that 10 percent of those older than 65 years had such mutations, compared with 1 percent younger than 50 years. The most frequent mutations in this study and in a similar study of 17,182 individuals in the United States and abroad5 were in the DNMT3A, ASXL1, and TET2 genes. Mutations in the genes JAK2, TP53, SF3B1, CBL, and SRSF2 were less common. Longitudinal follow-up of several cohorts revealed that individuals with clonal hematopoiesis exhibited an increased risk for development of hematologic cancers and all-cause mortality.

In 2015, we saw that these “seeds” could remain dormant, in a state of “clonal hematopoiesis of indeterminate potential (CHIP).” CHIP is defined as at least 2 percent variant allele frequency (VAF) of somatic mutations known to be associated with hematopoietic neoplasms, but without fulfilling diagnostic criteria for the malignancy (e.g., MDS or AML).1-4 There is a 0.5 to 1 percent risk of progression to overt malignancy per year (Figure), with increased rates in patients with a higher VAF of the somatic mutation.

Instead of remaining dormant, such clones may demonstrate opportunistic tendencies. In patients undergoing chemotherapy, clones may expand under the selective pressure of treatment and contribute to the development of therapy-related MDS or AML (t-MDS/t-AML).1 Historically, it was believed that chemotherapy and radiation led to therapy-related hematologic cancers because of increased numbers of mutations induced by treatment. However, contrary to this dogma, Dr. Terrence Wong and colleagues5 analysis of t-AML patient samples showed that there was not an increased number of mutations compared with de novo AML. Moreover, the same AML-associated mutations could be detected long before the diagnosis of cancer, and resistant clones simply expanded after treatment of the cancer.6 For example, in one patient with Hodgkin lymphoma, two TP53 mutations were detected in leukapheresis samples at a VAF of 0.5 percent six years prior to development of t-AML, and both TET2 and NPM1 mutations subsequently arose as potential driver mutations, only detectable later at the time when the leukemia was diagnosed.

Notably, two of the three most commonly observed mutated genes in normal individuals, DNMT3A and TET2, were also found to be the most frequent mutations that failed to clear by day 30 after induction chemotherapy for AML. Patients in whom these mutations persist exhibit a worse outcome, even in complete remission.6 Clearly, these mutations are not always innocuous. It will be our task as hematologists to contextualize the prognostic importance of these molecular abnormalities, not only patients with MDS or AML, but also in individuals with mild cytopenias or dysplasia of unknown significance (ICUS or IDUS, respectively) who do not meet diagnostic criteria for MDS. And what do we tell the otherwise normal individual who is referred to our clinic with one or more “hits” uncovered on a myeloid gene panel that should not have been ordered in the first place? We have much to learn ourselves before we can confidently guide patients through this maze of genetic complexity.

Dr. Becker indicated no relevant conflicts of interest.

Elotuzumab is a humanized recombinant IgG1 MoAB that targets signaling lymphocyte activation molecule (SLAMF7), also known as CS1 (CD2-subset-1). In a phase III study, elotuzumab, in combination with lenalidomide and dexamethasone in patients with relapsed disease, significantly extended progression-free survival (PFS) for patients (Pxs) with relapsed and/or refractory multiple myeloma (RRMM); the phase 3 tormilina-MM1 study (NCT01102431) was published in the New England Journal of Medicine (N Engl J Med). 2015;373:1207-1219.


Continuing the theme of immuno-oncology, data from solid tumor patients undergoing CAR-T cell therapy directed against CD19 suggested their potential to turn off anticoagulation almost instantly, like flipping a light switch. 4

The direct oral anticoagulants (DOACs) dabigatran, rivaroxaban, apixaban, and edoxaban, are associated with reduced major bleeding, intracranial hemorrhage, and fatal hemorrhage. However, reversal of anticoagulation is often required in patients undergoing surgery or undergoing emergency procedures. Although several approaches have been explored to reverse the anticoagulant effect of DOACs, reversal remains to be proven. Continued progress in the field of DOAC reversal in 2015 and beyond is expected to shed light on this and other challenges facing months of administration. 5

A remarkable feature of DOAC reversal agents is the rapidity with which their pharmacodynamic parameters change. Patients are at risk of full reversal of the anticoagulant effect of warfarin by vitamin K or plasma. Correction is achieved more quickly with prothrombin complex concentrate, but 40 percent of patients have a persistently elevated INR (1.4-3.0) minutes after infusion. 6 In contrast, DOAC-reversal agents correct coagulation tests within minutes of administration, suggesting their potential to turn off anticoagulation almost instantly, like flipping a light switch. Whether the effect of DOAC reversal agents on laboratory endpoints and clinical outcomes remains to be proven. Continued progress in the field of DOAC reversal in 2015 and beyond is expected to shed light on this and other challenges facing months of administration. 7

Not far behind idarucizumab in development is andexanet alfa, a first-in-humans clinical trial of REVERSED AD. Idarucizumab was approved in the United States and Europe in autumn of 2015 and is now the standard of care for emergency dabigatran reversal in jurisdictions where it is available.

Not far behind idarucizumab in development is andexanet alfa, a recombinant Fab fragment that binds and neutralizes dabigatran. Andexanet was well tolerated. Plasma samples from some subjects showed increased D-dimer and prothrombin 1+2 fragments.4 The clinical relevance of this observation remains to be determined.

Dr. Yee, O'Donnell, and Rajie indicated no relevant conflicts of interest.


The direct oral anticoagulants (DOACs) dabigatran, rivaroxaban, apixaban, and edoxaban, are associated with reduced major bleeding, intracranial hemorrhage, and fatal hemorrhage. However, reversal of these agents may be warranted in patients who have serious bleeding or who require an emergent procedure.

At this time last year, there was no standard of care for emergent DOAC reversal. Hospital committees grappled with low-quality evidence and conflicting guidelines for DOAC reversal. Clinicians lacked guidance on how to manage patients. The best available options, prothrombin complex concentrate, and activated prothrombin complex concentrate, were supported primarily by data from animal and human volunteer studies, and raised concerns about thrombotic risk. No data were available on the efficacy and safety of these agents in DOAC-treated patients with a clinical indication for emergent reversal. 2


In 2015, the vast majority of patients with Hodgkin lymphoma (HL) will be cured of their disease using standard treatments. Despite high rates of long-term disease control, late therapy-related toxicities (most importantly, secondary malignancies and cardiovascular disease) remain a source of significant morbidity and mortality among survivors. In 2015, results from a trio of important risk-adapted trials in early-stage HL were reported on, designed to maintain efficacy while reducing the risk of late effects. All three trials took the approach of using interim positron emission tomography (PET) scanning to determine how well treatment was working, allowing escalation of therapy for individuals in whom the initial response appeared poor, or reduction of therapy for those with an early metabolic response.

In the RAPID trial from the United Kingdom (Figure 1), patients with newly diagnosed stage Ia and IIa nonbulky HL underwent PET imaging after three cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine). PET-negative patients received an additional cycle of ABVD followed by IFRT. Patients who were PET-negative, defined by a Deauville score of 1 or 2 (fluorodeoxyglucose [FDG] uptake was less than the mediastinal blood pool) were randomized to no further therapy versus involved-field radiation therapy (IFRT) to 30 Gy. The randomization was designed to exclude a 7 percent or greater difference in three-year progression-free survival (PFS) between the two arms. After two cycles of ABVD, 75 percent of patients were PET-negative, and 420 patients were ultimately randomized. Although the 95 percent CI for the difference in risk crossed 7 percent (−8.8% to +1.3%), the outcome in both arms was excellent, with a three-year PFS of 94.6 percent in the radiotherapy (RT) arm versus 30.8 percent in the observation arm. There was no difference in overall survival.1

Preliminary results of the U.S. Intergroup study (Figure 2) of risk-adapted therapy in patients with nonbulky stage I and II classical HL were presented at the 57th ASH Annual Meeting in December.2 In this study, Deauville scores of 1 to 3 (FDG uptake less than liver) were considered negative. Patients who were PET-negative after two cycles of ABVD received two more cycles without RT. Individuals who were PET-positive were treated with two cycles of escalated BEACOPP (doxorubicin, bleomycin, vincristine, and dacarbazine) followed by IFRT to 30 Gy. The group treated 164 patients, 91 percent of whom were PET-negative. With a median follow-up of two years, the estimated 3-year PFS was 92 percent in the PET-negative arm. In the PET-positive group, the estimated three-year PFS was 66 percent.2 This figure may seem lower than the PET-positive arm of RAPID, where one further cycle of ABVD followed by 30 Gy IFRT yielded 87 percent PFS at five years, but it is important to note that the “PET-positive” group in that trial contained 90 patients with a Deauville score of 3, from a total of 145, which is likely to have increased the PFS substantially.

During the 13th International Conference on Malignant Lymphoma in June 2015, results from the H10 study by the European Intergroup (EORTC/LYSA/FIL; Figure 3) were presented.3 Patients with stage I and II disease were randomized between PET-adapted therapy and standard treatment with ABVD for three cycles (favorable) or six cycles (unfavorable) of ABVD. PET-negative patients received intensified therapy with escalated BEACOPP for two cycles followed by INRT to 30 Gy. In the PET-adapted arm, PET-negative patients (Deauville score of 1–3) received a total of four cycles (favorable) or six cycles (unfavorable) of ABVD. Interim PET-positive patients received intensified treatment with escalated BEACOPP for two cycles followed by INRT to 30 Gy. In total, 1,590 patients were enrolled, and interim PET was positive in 11 percent and 22 percent for the favorable and unfavorable groups, respectively. With a median follow-up of 4.5 years, among 361 patients who were PET-positive, the 5-year PFS was 91 percent in those on the PET-adapted arm who received BEACOPP, compared with 77 percent in the standard ABVD group. There was also a trend toward improved overall survival in the PET-adapted arm: 96 percent compared with 89 percent (p=0.062).3

These three studies demonstrate the utility of interim PET imaging as a biomarker in patients with early-stage HL. Overall, they suggest that escalation of chemotherapy for PET-positive patients is effective, and they provide evidence to support the idea of omitting RT for those with an early metabolic response. This does not seem to compromise overall survival, though there is a small increase in the risk of recurrence. It is notable that in all three studies the proportion of patients dying from HL was less than 3 percent overall, emphasizing the need to take a holistic view of the data and not focus exclusively on disease control.

Many hematologists/oncologists and patients alike are willing to accept a small increased likelihood of disease recurrence to avoid the risk of secondary cancers and cardiovascular disease associated with RT. To identify patients who may benefit from intensified or novel approaches, interim PET, and possibly molecular predictors, such as the recently described gene expression signature, may be useful tools.4 Additionally, with the availability of novel agents with impressive activity, such as brentuximab vedotin and nivolumab, therapeutic options for high-risk patients will continue to evolve, and trials of these approaches are already underway.

Acquired aplastic anemia (AA) results from autoimmune destruction of hematopoietic progenitor cells, and a significant proportion of these patients develop a myelodysplastic syndrome (MDS) and/or acute myeloid leukemia (AML) as a late complication of their disease. Recent studies have demonstrated clonal hematopoiesis (CH) in the majority of cases of AA, including pediatric patients and those in whom MDS and AML do not ultimately develop, and these clones are generally detectable early in the course of the disease. The distribution and types of mutations (frame-shift, nonsense, and splice site changes) identified in AA show significant overlap with those observed in association with MDS and AML but with a much lower allelic burden in the former. Comparison of diagnostic samples with those obtained six months from immunosuppression shows no significant difference in the numbers of different mutations present; the levels, however, are significantly increased after treatment.

The specific genes involved in AA show significant differences from, but also a good deal of overlap with, MDS and AML. Alterations of BCOR, BCORL1, and PIGA are more prevalent in AA, while JAK2, RUNX1, TET2, and TP53 are less so. Mutations of DNMT3A and ASXL1 are noted in both. Dr. Tetsuichi Yoshizato and colleagues suggest discrete mechanisms of clonal selection at play in these processes. In other words, CH in general seems to originate from a small clone that is present early in the disease course, and its evolution is dependent on the progressive accumulation of additional mutations and subsequent clonal selection. Thus, CH appears to signify leukemogenesis at a very early stage.

It is generally accepted that stem cells in all tissues, including the bone marrow, tend to accumulate somatic mutations over time, most of which are of no clinical significance. Occasionally though, a disease-initiating alteration occurs. Recent studies suggest that clones with mutations in certain genes seem to have a survival advantage in bone marrow failure. This occurs to vary through either escape from immune-mediated destruction, as with loss-of-function mutations in HLA class I genes, from a relative increase in proliferation, or both.

An understanding of the genes involved can provide some insight into the mechanism of disease. For instance, the most commonly detected mutation in these series results in a loss of function of DNMT3A, which impedes stem cell differentiation and results in accumulation of the abnormal cells within the bone marrow. TET2 mutations (also one of the most frequently identified) facilitate self-renewal and give rise to a competitive growth advantage. It is worth noting that candidate driver mutations, alterations that occur in a subset of genes known to be drivers of hematopoietic neoplasms, are relatively rare among young patients with AA and seem to be enriched in older individuals.

The differences in involved genes are not only of interest for understanding the evolution of disease, but some have also been shown to have prognostic implications. For instance, BCOR, BCORL1, and PIGA mutations generally portend a better response to immunosuppressive therapy and improved overall survival, while abnormalities of ASXL1, CSMD1, DNMT3A, RUNX1, and TP53 tend to herald inferior treatment response and shortened survival. In a similar vein, clones with aberrancies in the former (good prognostic) group of genes tend to remain small or diminish in size over time, whereas clones involving mutations of the latter (poor prognostic) group are more likely to grow in size and progress to MDS and/or AML.

On the clinical front, data presented at the 57th ASH Annual Meeting continue to highlight the promise of the eltrombopag in patients with severe AA. The rationale for using this agent is based on the expression of c-mpl, the receptor for thrombopoietin, on hematopoietic stem and progenitor cells, and the finding that the addition of recombinant thrombopoietin expands the pool of these cells in culture. In 2012, Drs. Cynthia Danubar and Neal Young, and colleagues from the National Institutes of Health (NIH) showed that eltrombopag elicited a 44 percent response rate, including multilineage responses, in patients with severe AA (sAA) refractory to immunosuppression. This led to U.S. Food and Drug Administration approval of eltrombopag in this patient population. In the Late-Breaking Abstracts session, Dr. Danielle Townsley, on behalf of colleagues from the same NIH group, presented data that extended these initial results. She presented data from a phase II trial of 88 treatment-naïve sAA patients, where eltrombopag was added to horse antithymocyte globulin (ATG) and cyclosporine (CSA). Ertrombopag was administered starting at day 14 (due to potential concerns for liver toxicity) for six months (cohort 1) or three months (cohort 2), or from day 1 for six months (cohort 3). The combination was well tolerated, and no increased marrow fibrosis was observed. Among the three treatment cohorts, the combination of eltrombopag with ATG + CSA yielded overall response rates at three and six months of 80 percent and 85 percent, respectively; complete response rates were 28 percent and 34 percent at these time points. The addition of eltrombopag yields response rates that are 20 percent to 30 percent higher than historical rates with ATG + CSA alone in sAA (p = 0.001). Clonal cytogentic evolution occurred in seven of 88 patients, similar to prior rates observed with standard immunosuppression. No baseline factors were predictive of outcome.

2015 was a breakthrough year for AA. The marriage of clinical breakthroughs with a more sophisticated understanding of the mutational landscape of AA is certain to catalyze robust translational research opportunities moving forward. Additional investigation is needed to correlate both baseline mutation status and temporal changes in clonal architecture (Figure) with disease natural history and response to immunosuppression and hematopoietic stem cell transplantation.
New Therapeutic Frontiers in Sickle Cell Disease

CHARLES T. QUINN, MD, MS
Associate Professor of Clinical Pediatrics, University of Cincinnati College of Medicine and Cincinnati Children’s Hospital Medical Center, Cincinnati, OH

A panoply of potential new therapies for sickle cell disease (SCD) has emerged in just the past five years. Pharmaceutical companies are now actually interested in SCD. Many small biotech firms now run more than one clinical trial at the same time, and even decline participation in others because of limited resources and competing enrollment. For example, in March 2015, the Blood column highlighted three publications from 2015 that reported new therapeutic frontiers in different stages of development: gene therapy, antiadhesive therapy, and modulation of coagulation.

Gene therapy for SCD has always been ‘just around the corner.’ Now it is actually here for humans, albeit in an extremely limited and experimental basis. Five individuals with SCD have undergone some form of gene transfer therapy to date, but the durability of clinical benefit of the current generation of gene therapy methods remains to be demonstrated. Even so, next-generation gene therapy techniques are already being studied in preclinical models. An ideal gene therapy for SCD would avoid the problems of insertional mutagenesis and difficulty achieving proper spatiotemporal expression of a transgene by permanently correcting the sickle mutation in situ. In an effort to achieve this goal, Dr. Megan Hoban and colleagues used specifically engineered zinc-finger nucleases and a donor nucleic acid to correct the sickle mutation in hematopoietic stem and progenitor cells (HSPCs).1 These modified HSPCs could engraft in immunodeficient mice. Clearly, more work needs to be done until the definitive evidence emerged from one or more prospective, randomized controlled trials.

The first myth consists of the idea that patients who are anticoagulated for so-called high-risk (but hemodynamically stable) pulmonary embolism (PE) might benefit from the placement of a retrievable inferior vena cava filter (IVC filter). Indeed, the general notion that more aggressive interventions (over and above anticoagulation therapy) might benefit high-risk PE patients is not new. For example, more than one randomized controlled trial of thrombolysis plus anticoagulation versus anticoagulation alone has been conducted in this population. For some individuals with SCD, who are anticoagulated for so-called high-risk (but nonmalignant hematology world were busted (to use a verb from the title of a recently popular television series, “MYTH BUSTERS”). In both cases, the myth was based on biological theory and observational data from uncontrolled studies, while the definitive evidence emerged from one or more prospective, randomized controlled trials.

During 2015, two important myths from the nonmalignant hematology world were busted (to use a verb from the title of a recently popular television series, “MYTH BUSTERS”). In both cases, the myth was based on biological theory and observational data from uncontrolled studies, while the definitive evidence emerged from one or more prospective, randomized controlled trials.

The second myth to be challenged was that, among patients who receive so-called ‘fresher’ units of packed red blood cells (RBCs) fare better than patients who receive RBC units of ‘standard’ age. This idea that fresher blood might be better has a basis in biology2 and observational data.3 However, in 2015, two randomized trials involving a cumulative total of 395 patients failed to demonstrate any evidence of a mortality (or other clinical) benefit among those who received ‘fresher’ RBCs. In one study, the mean ages of RBCs were six versus 22 days, and in the other, the median ages were seven versus 28 days. The studies involved critically ill adult patients and patients (12 years or older) undergoing complex cardiac surgery; all RBCs were administered leukoreduced. Like any data from a clinical trial, the evidence provided by these large trials can certainly be criticized. What if more RBC units older than 35 days had been tested? Should the variable of interest (age of RBCs) have been treated as a random variable rather than as a fixed variable? Would the estimated treatment effect be different in different subgroups? We need more data from well-designed clinical trials to answer these questions.

Since the 1960s, the idea that fresher blood might be better has been popular among some hematologists and surgeons. The myth gained credibility because it was based on biological theory and observational data from uncontrolled studies, while the definitive evidence emerged from one or more prospective, randomized controlled trials.

The myth was based on biological theory and observational data from uncontrolled studies, while the definitive evidence emerged from one or more prospective, randomized controlled trials.

Dr. Quinn indicated no relevant conflicts of interest.

Therapeutically Enhancing Stem Cell Engraftment

JONATHAN HOGGATT, PhD
Assistant Professor, Cancer Center and Center for Transplantation Sciences, Massachusetts General Hospital/Harvard Medical School, Boston, MA

A multipronged approach in global efforts to eliminate this human host and the mosquito vector of malaria has contributed to a dramatic global decline in malaria since 2000 and to the reduction of the global burden of the disease. Malaria parasites are transmitted to humans by the female Anopheles mosquito, which feeds on blood, entering the human host and the mosquito vector through the bite. The cycle of malaria begins with the mosquito叮咬 human host, infecting the red blood cells and multiplying the parasite, which is transmitted back to the mosquito during feeding. Once in the liver, the parasite infects the hepatic cells and multiplies, leading to the development of a new mosquito vector.

In the liver, the parasite infects the hepatic cells and multiplies, leading to the development of a new mosquito vector. Once mature, the parasites are released into the bloodstream, infecting new red blood cells and replicating. This process continues, resulting in an explosive increase in the number of infected red blood cells, leading to the clinical manifestations of malaria.

Several interventions have been used to control malaria, including the use of insecticide-treated bed nets and indoor residual spraying with insecticides. These interventions, followed by immediate and appropriate treatment of the patient, have contributed to a dramatic global decline in malaria since 2000 and to the achievement of the United Nations’ Millennium Development Goal by 2015.1

Despite this progress, 3.2 billion people remain at risk of contracting malaria. According to the latest World Health Organization report,1 an estimated 214 million new cases and approximately 438,000 deaths were reported in 2015. Sub-Saharan Africa continues to bear the brunt of the disease, accounting for 88 percent of the morbidity and 90 percent of the mortality, mainly in children younger than five years.

The gains that have been achieved are threatened by the development of insecticide resistance in African vector species and by the alarmingly rapid development and spread of drug-resistant parasites, which have rendered several antimalarial drugs useless. Resistance to artemisinin by Plasmodium falciparum, the most deadly of the five species of Plasmodium parasites that infect humans, has recently been detected in five countries in the Greater Mekong region. This threat has accelerated the research into the biology of P. falciparum and its interaction with the human host, and has fueled efforts to develop new drugs and a vaccine. Several major advances have been reported this year, and results from four studies are highlighted here.

In a multi-institutional collaboration2 led by Dr. Kasturi Haldar, the specific glycosylated target of artemisinin in early-ring stage P. falciparum was identified as phosphatidylglycerolamine.3 This finding has implications for the development of new anti-malarial drugs and vaccines, as well as for the understanding of the mechanisms by which artemisinin exerts its therapeutic effects.

Malaria: Progress in the Host-Pathogen Arms Race

THERESA COETERZEE, PHD
Co-Director of the Wits Research Institute for Malaria; Associate Professor, University of the Witwatersrand, Johannesburg, South Africa

The 2015 Nobel Prize in Physiology or Medicine was awarded to three scientists for their discoveries on novel therapies against parasitic infections. Youyou Tu from China was honored for isolating artemisinin, the active ingredient from the Chinese herb Artemisia annua, which rapidly kills malaria parasites. Artemisinin combination therapy is the current gold standard treatment for malaria, and it has had a major impact on diminishing the burden of the disease. Malaria parasites are transmitted to humans by female Anopheles mosquitoes, and, after initial replication in the liver, they invade and subsequently destroy red blood cells (RBCs), which triggers the clinical symptoms of the disease. The complex parasite lifecycle in both the human host and the mosquito vector has necessitated a multipronged approach in global efforts to eliminate this remarkably successful pathogen. Preventive measures, including the use of insecticide-treated bed nets and indoor residual spraying with insecticides, have been combined with rapid diagnostic test kits in order to detect malaria as early as possible. These interventions, followed by immediate and appropriate treatment of the patient, have contributed to a dramatic global decline in malaria since 2000 and to the achievement of the United Nations’ Millennium Development Goal by 2015.1

While the 11,12-EET strategy followed the aforementioned contributions to therapeutic enhancement of stem cell engraftment, many researchers have explored the role of eicosanoids, including 11,12-epoxyeicosatrienoic acid (11,12-EET) and 14,15-EET, which are derived from arachidonic acid (AA) by the cytochrome P450 epoxygenases (Figure). Two articles in 2015 have now expanded the focus on inhibiting COX enzyme activity to decrease prostaglandin (PG) and prostacyclin (PGI2) levels. However, as PGE2 enhances stem cell

Phosphatidylglycerolamine (PG) is a novel target for drug development, as it is essential for the survival of P. falciparum in the liver stage of infection. Inhibition of the prostaglandin-degrading enzyme 15-PGDH potentiates tissue regeneration. Science. 2015;348:aaai2340.


The Hematologist: ASH NEWS AND REPORTS

Figure

Archachidonic Acid Cascade

Shown is a simplified version of the arachidonic acid cascade. After arachidonic acid is released by phospholipase A2, it can then be converted to numerous other eicosanoid molecules by a variety of eicosanoid enzymes. Cyclooxygenases enzymes convert arachidonic acid into thromboxanes, prostacyclins, and prostaglandins, notably Prostaglandin E2. These enzymes are the target of many nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen. Prostaglandin E2 is then rapidly degraded by 15-hydroxyprostaglandin-dehydrogenase (15-PGDH), which is the target of the small molecule inhibitor SW033291. Arachidonic acid can also be converted into leukotrienes, many of which are mediators of allergy, and into the epoxyeicosatrienoic acids (EETs) by the cytochrome P450 epoxygenases.

Dr. Hoggatt indicated no relevant conflicts of interest.


A New Roadmap for Optimizing Thiopurine Therapy in Acute Lymphocytic Leukemia

ELIZABETH RAETZ, MD, AND JULIA MEYER, PhD

1. Professor, in the Division of Pediatric Hematology/Oncology; Director of High-Risk Leukemia and Lymphoma Program, University of Utah/Huntsman Cancer Institute, Salt Lake City, UT
2. Postdoctoral Fellow, University of Utah School of Medicine, Salt Lake City, UT

The treatment of childhood acute lymphocytic leukemia (ALL) has been a success story with the majority of patients now achieving cure; however, there is still a steep learning curve with regard to our understanding of how to most effectively and safely deliver conventional chemotherapeutic drugs. The bulk of childhood ALL therapy is the approximately two-year program, the backbone of which is daily administration of 6-mercaptopurine (6MP). Questions still remain regarding how best to fine tune dosing of 6MP in individual patients and how to enhance compliance with daily oral 6MP during the several-year trajectory of an ALL treatment course. Further, despite overall high cure rates for childhood ALL, some patients develop resistance to 6MP; efforts at early detection of resistance are underway, so preemptive changes can be made to avert relapse. 6MP has been a mainstay of ALL therapy for the past six decades; however, three seminal articles published in 2015 lent critical insights into why optimal delivery of this drug is critical to the success of patient outcomes.

Expanding on prior studies, which have demonstrated that nonadherence to 6MP increases relapse risk, Dr. Smita Bhata and colleagues reported their results from a large prospective multivariate study examining the effects of high intra-individual variability of 6MP exposure on the risk of relapse.1 The authors assessed adherence in 742 children throughout a six-month period during the maintenance phase of therapy on Children’s Oncology Group (COG) treatment regimens. The authors observed that patients with a mean 6MP adherence rate of less than 95 percent were at a 2.7-fold increased risk of relapse compared with those having 95 percent or greater adherence. Adherence was measured in this study using a special bottle cap with an electronic monitoring device to record the date and time of bottle opening for medication administration. The authors examined several other variables related to mediation adherence to determine their impact on relapse risk, including erythrocyte thiosemine (TGN) levels, 6MP dose intensity (number of prescribed 6MP doses divided by the number of planned protocol doses), thiosemine mRNA levels (TPMT genotype), and neutrophil count (ANC). Interestingly, dose intensity and TGN levels were not associated with the risk of relapse. Notably, however, among adherent patients, high intra-individual variability of 6MP exposure increased the risk of relapse by 4.4 fold. This variability in TGN levels was the result of varying 6MP dose intensity and drug treatment interruptions.

These findings raise important questions about how best to adjust 6MP dosing during ALL maintenance therapy. Presently, in COG protocols, 6MP dose adjustments are made in an effort to target an ANC range of 1.5 to 5.0 × 10^9/L and a platelet dose of 100 × 10^9/L, respectively. Once blood counts recover, 6MP is reintroduced at a reduced dose with incremental dose increases, as tolerated. Patients tend to experience fluctuations in their blood counts that require 6MP dosing modifications, and given the association of TGN variability and relapse, this raises the question of whether current dosing guidelines should be considered in an effort to reduce drug interruptions and maintain more consistency in TGN levels.

The work by Dr. Bhata and colleagues also ties in well with other influential reports this year describing a new host polymorphism impacting tolerance of 6MP and new discoveries on the role of thiopurine resistance. While adherence to 6MP is key to minimizing relapse risk, understanding how inherited variants contribute to 6MP intolerance is also important so that consistent exposure can be maintained and excessive toxicity can be avoided. In early 2015, Dr. Jun Yang and colleagues identified a novel germline variant in the gene NUDT15, which was strongly associated with 6MP intolerance and which was most frequently found in patients of East Asian and Hispanic descent.2 The newly identified variant is hypothesized to lead to a loss-of-function phenotype for NUDT15, causing extensive DNA damage and cytotoxicity. Patients that were homozygous for the TT genotype tolerated 8.3 percent of planned 6MP doses. This discovery, coupled with existing data on the role that TPNM variant alleles also play in 6MP intolerance,3 will help to identify a significant number of children spanning different racial and ethnic groups for individualized 6MP dosing.

Since the first reports that relapse-specific acquired mutations in the gene NTC2 cause overt resistance to 6MP,4,5 two new studies published in 2015 have helped to expand our knowledge of genes contributing to thiopurine resistance. Dr. Xiaolu Ma and colleagues showed that the prevalence of mutations in NTC2 may be as high as 45 percent in patients with early ALL relapses, and further, that these mutations were often acquired in the founding relapse clone.6 They also observed that patients can acquire multiple mutations in NTC2, with some patients bearing multiple mutations in both TGN levels and genotype, demonstrating the selective pressure on leukemia cells to evade 6MP cytotoxicity. Additionally, Dr. Bhasharg Li and colleagues reported that NTC2 resistance can occur through the acquisition of relapse-specific mutations in the gene BPFS.7,8 BPFS is an enzyme involved in the de novo purine synthesis pathway and the acquired mutations were shown to reduce nucleotide feedback inhibition, causing a reduction in the conversion of 6MP into its active metabolite. Mutations were found in 6.7 percent of the B-lineage ALL samples examined and were mutually exclusive of NTC2 mutations. Taken together, these studies suggest that resistance to 6MP is a commonly observed mechanism of ALL relapse.

While continued advances in the field of pediatric ALL are envisioned with precision medicine initiatives and the development of new targeted agents, the improved utilization of thiopurine therapy drugs also falls within the spirit of these efforts. The report by Dr. Bhata and colleagues and the aforementioned studies published in 2015 converge on a central theme of employing different approaches to optimize thiopurine delivery during ALL maintenance therapy (Figure). These studies raise important considerations for the development of future prospective ALL trials and suggest that measures to enhance adherence and reduce treatment interruptions will need to be carefully considered. In concert, prospective assessment for TPMT and NUDT15 variants to identify individuals at risk for 6MP toxicity.

Figure

**Strategies for optimizing the delivery of thiopurine therapy**

**Table**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Host TPMT and NUDT15 Genotyping</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6. RTS,5 Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine candidate RTS,S/AS01. More than 15,000 controlled phase III trial on the most advanced malaria vaccine candidate RTS,S/AS01. More than 15,000 vaccinated were at a 2.7-fold increased risk of relapse compared with those having 95 percent or greater adherence. Adherence was measured in this study using a special bottle cap with an electronic monitoring device to record the date and time of bottle opening for medication administration. The authors examined several other variables related to medication adherence to determine their impact on relapse risk, including erythrocyte thiosemine (TGN) levels, 6MP dose intensity (number of prescribed 6MP doses divided by the number of planned protocol doses), thiosemine mRNA levels (TPMT genotype), and neutrophil count (ANC). Interestingly, dose intensity and TGN levels were not associated with the risk of relapse. Notably, however, among adherent patients, high intra-individual variability of 6MP exposure increased the risk of relapse by 4.4 fold. This variability in TGN levels was the result of varying 6MP dose intensity and drug treatment interruptions.

In conclusion, despite the major advances reported in these four studies, they have highlighted our lack of in-depth understanding of the complex interplay between the malaria parasite and its human host. Numerous challenges remain and it will require an enhanced effort not only by researchers, but also by political leaders and funders, to ensure that the current momentum is not lost in the battle against this formidable pathogen.

Dr. Coetzer indicated no relevant conflicts of interest.

---

**Figure**

**Strategies for optimizing the delivery of thiopurine therapy**

1. Postdoctoral Fellow, University of Utah School of Medicine, Salt Lake City, UT
2. Professor, in the Division of Pediatric Hematology/Oncology; Director of High-Risk Leukemia and Lymphoma Program, University of Utah/Huntsman Cancer Institute, Salt Lake City, UT

---

6. RTS,5 Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine candidate RTS,S/AS01. More than 15,000 vaccinated were at a 2.7-fold increased risk of relapse compared with those having 95 percent or greater adherence. Adherence was measured in this study using a special bottle cap with an electronic monitoring device to record the date and time of bottle opening for medication administration. The authors examined several other variables related to medication adherence to determine their impact on relapse risk, including erythrocyte thiosemine (TGN) levels, 6MP dose intensity (number of prescribed 6MP doses divided by the number of planned protocol doses), thiosemine mRNA levels (TPMT genotype), and neutrophil count (ANC). Interestingly, dose intensity and TGN levels were not associated with the risk of relapse. Notably, however, among adherent patients, high intra-individual variability of 6MP exposure increased the risk of relapse by 4.4 fold. This variability in TGN levels was the result of varying 6MP dose intensity and drug treatment interruptions.

In conclusion, despite the major advances reported in these four studies, they have highlighted our lack of in-depth understanding of the complex interplay between the malaria parasite and its human host. Numerous challenges remain and it will require an enhanced effort not only by researchers, but also by political leaders and funders, to ensure that the current momentum is not lost in the battle against this formidable pathogen.

Dr. Coetzer indicated no relevant conflicts of interest.
Clinical Implications of Novel Regulatory Mechanisms for Neutrophils, and Erythrocytes

MARK J. KOURY, MD
Professor of Medicine, Vanderbilt University, Nashville, TN

Several 2015 publications involving mouse models that examined blood counts and neutrophil and eosinophil hematopoietic events have advanced our understanding of both steady-state hematopoiesis and production rates for platelets, neutrophils, and erythrocytes. These studies provided insights that were specific to each of the three blood cell lineages. The newly identified regulatory mechanisms suggest potential new approaches for treating diseases that result in abnormal numbers of platelets, neutrophils, or erythrocytes.

A newly described mechanism for rapid platelet production, which occurs in emergency situations such as low circulating platelet levels due to enhanced destruction or increased platelet numbers from intense inflammation or infection, is megakaryocyte rupture induced by G-CSF (14-15). Sudden IL-1α-mediated release of larger-than-normal platelets increases production rates by more than an order of magnitude over the proplatelet shearing mechanism of steady-state platelet production. Both of these release mechanisms require development of mature megakaryocytes located adjacent to the vascular sinuses of the marrow, a process regulated by thrombopoietin (TPO). The principal growth factor for megakaryocytes that is produced mainly by the liver. Aging of circulating platelets has been associated with desialylation of surface glycoproteins, which in turn leads to platelet removal from the circulation after binding to glycoprotein receptors on other blood cells. This ROS-mediated emergency granulopoiesis is related to the successful neutrophil and monocyte production in response to increased TPO levels in situations such as sepsis or trauma.

Despite brief intravascular life spans, neutrophils were found to age in the circulation in response to products of the granulocyte colony-stimulating factor (G-CSF). Therefore, it has been hypothesized that the potential therapeutic benefit provided by G-CSF may involve a direct synergistic interaction between desamethasone and peroxisome proliferator-activated receptor-α (PPAR-α), whereas expression of EPO-dependent erythroid progenitors, common to both G-CSF and PPAR-α-regulated pathways, did not involve PPAR-α. The mechanisms regulating erythropoiesis may be more related to the PPAR-α pathway, suggesting that future treatments to increase erythropoiesis may involve PPAR-α agonists. However, a recent report suggests that increased EPO responsiveness of erythroid cells, in which defective myeloid leukocyte activity increases susceptibility to bacterial infections. Transferrin receptor-2 (TFR2) plays a role in the absorption of iron that is transferred from transferrin to transferrin receptor. Iron deficiency, instability of unbound TFR2 leads to increased iron absorption and flux via decreased hepcidin and increased EPO responsiveness of erythroid cells. The method by which increased EPO responsiveness coordinates with other regulators of erythropoiesis in iron deficiency (such as iron regulatory protein-1 (IRP-1) limiting EPO production and heem-regulated iron importer (HR) limiting heemoglobin synthesis) is unknown, but multiple levels of control are present in the erythropoietic response to this common cause of anemia.

The emergency situation in anemia is tissue hypoxia, and the erythropoietic response to anemia is termed "stress erythropoiesis." Renal EPO production has been extensively studied in stress erythropoiesis. However, beginning at the burst-forming unit-erythroid (BFU-E) stage and extending to the proerythroblast stage of differentiation, non-EPO mediators such as glucocorticoids, stem cell factor, and an iron-responsive growth factor-α, can expand erythropoietin progenitor cell populations without inducing differentiation. Glucocorticoid-induced expansion of BFU-Es was shown to involve a direct synergistic interaction between desamethasone and peroxisome proliferator-activated receptor-α (PPAR-α), whereas expression of EPO-dependent erythroid progenitors, common to both G-CSF and PPAR-α-regulated pathways, did not involve PPAR-α. The mechanisms regulating erythropoiesis may be more related to the PPAR-α pathway, suggesting that future treatments to increase erythropoiesis may involve PPAR-α agonists. However, human urokinase is a combination of an enzyme that degrades fibrin and a heparin-like compound that inhibits platelet aggregation.

Dr. Dorothea Zucker-Franklin, MD (1929 – 2015)

Dr. Dorothea Zucker-Franklin, National Academy of Medicine member, pioneer in electronic microscopy of blood cells at New York University School of Medicine, and third female president of ASH (1995), passed away November 24, 2015, at the age of 86. Dottie was born in Berlin, Germany, but fled to the Netherlands with her family in 1933 to escape Nazism. There she attended the same school as Anne Frank and was forced into hiding in 1943. Arriving destitute in New York in 1948, Dottie graduated from Hunter College as class valedictorian and proceeded to become the first American woman to receive a medical degree. She founded and directed the hematology program at New York University School of Medicine, and was named the inaugural holder of the Gertrude Elion Chair in Hematology and Oncology. She was the first female president of ASH (1995). Dottie’s later studies explored electron microscopy and the role of the hemolytic process in blood cell destruction, particularly in the autoimmune hemolytic anemias, type I diabetes mellitus, and other blood disorders. Dottie’s contributions to the field of hematology and her role as a pioneer for women in medicine were recognized with numerous awards and honors, including the National Institutes of Health Distinguished Scientist Award, the American Society of Hematology Lifetime Achievement Award, and the Lifetime Achievement Award of the American Association for the Advancement of Science. Dottie’s legacy continues to inspire new generations of hematologists and scientists around the world. She is survived by her daughter, Dr. Mary Koury, and her grandchildren, Emily and Benjamin. The family is planning a memorial service in the fall of 2016. Memories of Dottie will be shared at the 2016 ASH Annual Meeting in Seattle. Donations may be made in memory of Dottie to the American Society of Hematology, 2025 L Street NW, Suite 600, Washington, DC 20036.
Pulmonary complications are a known contributor to mortality in adults with sickle cell disease (SCD). In this article, Dr. Adetola Kasim and colleagues present data examining the prognostic significance of decreased pulmonary function in a large prospective cohort of SCD patients in the Cooperative Study for Sickle Cell Disease. They confirm that a decreased forced expiratory volume in 1 second percent (FEV1 %) predicts for earlier death in patients with SCD. Surprisingly, obstructive or restrictive pulmonary function test abnormalities are not predictive of earlier death. Further study is needed to better understand the pathophysiology and negative impact of decreased FEV1 % in SCD patients.

Dr. Bob Lüwenberg (Editor-in-Chief) and Dr. Nancy Berliner (Deputy Editor-in-Chief) have combined efforts to identify some of the most outstanding Blood articles that have appeared either in print or online during the two-month interval between issues of The Hematologist. The goal is to underscore the remarkable research that is published in Blood and to highlight the exciting progress that is being made in the field.

SEPTEMBER 10, 2015


The Gardos channel is a Ca2+-sensitive potassium channel that is widely expressed in tissues and cells, including erythrocytes. It has been widely studied as a potential regulator of cell volume that may be important in hemoglobinopathies. In this week’s plenary papers, Dr. Raphael Rapetti-Mauss and colleagues and Dr. Edyta Glogowska and colleagues identify mutations in the KCNN4 gene, which encodes the Gardos channel, as the molecular basis for a subset of hereditary xerocytosis and chronic hemolytic anemia associated with dehydrated cells. These studies confirm the importance of the Gardos channel in maintaining erythrocyte hydration, and they offer a potential clinical entry point for treatment of this rare syndrome.

SEPTEMBER 17, 2015


Dr. Jean Donadieu and colleagues present the most promising treatment data to date in a group of patients with Langerhans cell histiocytosis (LCH) who historically have had a notoriously unfavorable survival. The investigators applied a standardized disease activity score to follow and evaluate these patients on therapy. They report their encouraging results of an intensive chemotherapy regimen of cladribine and cytarabine in a multicenter trial in children with disease of the bone marrow, liver, or spleen who were refractory to standard therapy.


Factor XIIa (FXIIa) and FXIIa contribute to thrombosis in animal models, while platelet-derived polyphosphate (polyP) may potentiate contact or thrombin-feedback pathways. Dr. Shu Zhu and colleagues discovered that platelet-derived polyP plays a significant role in human whole blood that is distinct from FXIIa activation and thrombin generation through feedback activation of FXI. polyP directly interacts with fibrin in a way that makes the thrombus less susceptible to lysis by thrombin inhibitors. The way in which FXIIa and polyP contribute to thrombus formation in human blood and the fact that blocking polyP reduces thrombus stability and increases lysis of the fibrin clot suggest that polyphosphate inhibitors are among the most interesting candidate antithrombotic therapeutic agents.

SEPTEMBER 24, 2015


A substantial proportion of patients with aggressive forms of mantle cell lymphoma develop central nervous system (CNS) metastasis, which is notoriously difficult to treat. In this article, Dr. Sophie Bernard and colleagues provide evidence that rituximab, an orally administered inhibitor of B lymphocyte tyrosine kinase, crosses the blood-brain barrier and has significant therapeutic activity in CNS disease of mantle cell lymphoma.

OCTOBER 1, 2015


In this week’s plenary papers, Dr. Raphael Rapetti-Mauss and colleagues and Dr. Edyta Glogowska and colleagues identify mutations in the KCNN4 gene, which encodes the Gardos channel, as the molecular basis for a subset of hereditary xerocytosis and chronic hemolytic anemia associated with dehydrated cells. These studies confirm the importance of the Gardos channel in maintaining erythrocyte hydration, and they offer a potential clinical entry point for treatment of this rare syndrome.

OCTOBER 22, 2015


Dr. Joan Gill and colleagues present the results of a phase III trial of recombinant von Willebrand factor (rVWF) for treatment of bleeds in patients with severe von Willebrand disease (VWD). Their results confirm that rVWF is safe and highly effective for the control of bleeding. Since patients with severe VWD are initially factor VIII (FVIII) deficient as well because VWF stabilizes FVIII, the first dose of rVWF was administered with FVIII. Later FVIII dosing proved to be unnecessary, as endogenous stores recovered upon administration of rVWF. Bleeding control was achieved in 97 percent of bleeds, and only one infusion was required in more than 80 percent of bleeding episodes. These encouraging results represent a major breakthrough in the treatment of VWD.


The appropriate oral treatment of iron deficiency is codified and rarely questioned, but perhaps it should be. In this article, Dr. Diego Moretti and colleagues report on a study of iron administration that is based on the current understanding of iron metabolism and may be practice-changing. Since serum iron levels are one factor regulating hepcidin, they postulate that absorption of iron supplements could paradoxically induce hepcidin and inhibit further iron absorption. Using a clever strategy of differing iron doses labeled with different Fe isotopes, they document that this is in fact the case. They demonstrate that iron supplements of 60 mg of iron or more increase hepcidin for up to 24 hours, impairing subsequent iron absorption. They suggest that alternate-day single doses of iron could improve the efficacy of oral iron therapy, allowing a welcome reduction in gastrointestinal side effects, confirmation awaits an appropriate clinical trial.

Dr. Bob Lüwenberg (Editor-in-Chief) and Dr. Nancy Berliner (Deputy Editor-in-Chief) have combined efforts to identify some of the most outstanding Blood articles that have appeared either in print or online during the two-month interval between issues of The Hematologist. The goal is to underscore the remarkable research that is published in Blood and to highlight the exciting progress that is being made in the field.

NOVEMBER 5, 2015


The PD-1/PD-L1 pathway inhibits host antitumor responses in a wide variety of malignancies. However, since PD-1 is normally expressed on lymphocytes within the lymph node, the potential role of this pathway in lymphoma is complex. Dr. Junichi Kiyasu and colleagues report an in-depth study of the expression of PD-1 and PD-L1 in diffuse large B-cell lymphoma (DLBCL) cells and the surrounding microenvironment. They demonstrate that 11 percent of DLBCLs manifest PD-L1 expression on the tumor cells and that this has a negative impact on overall survival. In contrast, expression of PD-L1 by infiltrating lymphocytes within the microenvironment does not affect survival. This suggests that targeting this pathway with checkpoint inhibitors may be a therapeutic option in this subset of DLBCL patients.


Chronic lymphocytic leukemia (CLL) is associated with hypogammaglobulinemia and immune dysregulation, which contribute to increased infections. The Bruton tyrosine kinase (BTK) inhibitor rituximab is a recently approved novel agent that induces a high rate of response in CLL. However, congenital loss of BTK results in Bruton agammaglobulinemia, a severe B-cell defect, suggesting that BTK is also critical to normal B-cell function. In this article, Dr. Clare Sun and colleagues assess the impact of rituximab on normal B-cell function in patients with CLL, and demonstrate that the BTK inhibitor allows partial reconstitution of normal B cells and humoral immunity at 12 months. Since patients are treated with Brutinib long-term, further follow-up is needed to assess the full extent of immune reconstitution and its impact on infectious outcomes.

NOVEMBER 12, 2015


This article resolves years of conflicting results regarding the inactivation of factor XIIa (FXIIa) by plasmin. Dr. WooSuk Hur and colleagues demonstrate that plasmin inactivates activated blood coagulation factor XIIa, but not zymogen factor XII (FXII). They also show that FXIIa is inactivated during clot lysis but not during clot formation.

NOVEMBER 19, 2015


Increasingly, clinicians are obtaining molecular genetic tests when evaluating patients with unexplained cytopenias. How is one to interpret the detection of clonal hematopoiesis in the absence of dysplastic changes in the bone marrow? Is a clonal mutation is discovered, yet diagnostic criteria for a hematological neoplasm are not met, what is the diagnosis? Dr. Brian Keow et al and Dr. Catherine Cago and colleagues report results of mutation testing in two series of patients with cytopenia and nondiagnostic marrows. These two plenary papers demonstrate that the answer is challenging and that the appropriate interpretation of positive mutation testing in patients without evidence of dysplasia is not straightforward.

The Hematologist: ASH NEWS AND REPORTS

15
WHAT’S ON THE WEB

As technology and the Web have evolved, so too have ASH’s online offerings. Now, beyond the ASH website, you can download ASH apps for your smartphone or tablet, follow ASH on Twitter (www.twitter.com/ASH_hematology), and find ASH videos on YouTube (www.youtube.com/user/ASHWebmaster).

Read The Hematologist online at www.hematology.org/thehematologist, and catch up on the latest news in the field of hematology right on your desktop, mobile phone, or tablet.

MARK YOUR CALENDAR

January

22-23 Highlights of ASH® in North America
Dallas, TX www.hematology.org/highlights

29-30 Highlights of ASH in North America
San Diego, CA www.hematology.org/highlights

February

18 2016 Clinical Research Training Institute in Latin America application due
Washington, DC www.hematology.org/awards

19 2016 HONORS Award applications due
Washington, DC www.hematology.org/awards

March

5-6 Highlights of ASH in Asia-Pacific
Brisbane, Australia www.hematology.org/highlights

7 2016 Minority Medical Student Award Program applications due
Washington, DC www.hematology.org/awards

18 Latin American Training Program applications due
Washington, DC www.hematology.org/awards

25 2016 Clinical Research Training Institute applications due
Washington, DC www.hematology.org/awards

31 Visitor Training Program applications due
Washington, DC www.hematology.org/awards

April

29-30 Highlights of ASH in Latin America
Natal, Brazil www.hematology.org/highlights

Just Released: The New ASH Pocket Guides App

ASH Pocket Guides, quick references covering nine key patient-care topics, are now available in a new mobile app!

The ASH Pocket Guides app includes interactive versions of all the Society’s clinical quick-reference guides. In addition to the pocket guide contents, the app includes tools to aid in clinical decision making, including bleeding score and 4Ts calculators, calculators for initial and chronic warfarin dosing, and interactive algorithms for the diagnosis and management of heparin-induced thrombocytopenia and von Willebrand disease.

The app is free to download and is available for iOS and Android devices. Visit www.hematology.org/pocketguidesapp for more information.

*Please be sure to download the new app, as this version completely replaces the previous ASH Guides app, and the older version will not automatically update to include the new content.