Editor’s Note: The following commentary represents the opinion of the Editor-in-Chief of The Hematologist and does not reflect any official position of the American Society of Hematology.

As we settle in for a Trump presidency, numerous political pundits are still trying to explain his unprecedented victory, and must conclude that the experts’ polling was as useful as shoe umbrellas. We’ve heard the parade of explanations: Hillary’s server and bleached emails, the James Comey effect, the revenge of the forgotten rust-belt worker, Trump as a swamp-draining agent of change, and failure to mobilize sufficient numbers of Democrats to the polls.

For voters banking on a Hillary win, including individuals tagged as “coastal liberal elites,” this postelection period is being used to claw through denial, anger, bargaining, depression, and acceptance. Incredulity persists regarding how the Oval Office will be turned over to a man who whipped up a salad of xenophobic populist fervor, misogyny, and racism, and dressed it with winks and nods to the self-described “alt-right.” However, our democracy rests on free and willing adults having every right to choose their political diet and make as many return trips to the buffet as they’d like. Trump voters would argue, and they may be right, that coastal elites live in a bubble, disconnected from the heartland and from the hearts and minds of those who live outside of New York, Washington, and San Francisco. Of course, it’s a lot more complicated than this.

As a guest on MSNBC’s “Meet the Press Daily,” republican strategist Brad Todd offered a snappy idiom to both explain Trump’s tractions amongst voters as well as journalists’ inability to pin him down on issues: “The voters take Donald Trump seriously as a candidate but they don’t take him literally; the press takes Donald Trump literally but they don’t take him seriously…” Todd’s rubric was widely disseminated among media outlets that latched on to this as both an epiphany and perhaps the prologue to a user’s manual on how to adapt to Trump as a new breed of politician. Todd aptly pointed out that both politicians and journalists are wordsmiths devoted to ensuring that the tone and meaning of words are parsed over countless times by seasoned political operatives in the case of politicians, and by a hierarchy of editors and fact-checkers in the case of journalists. We hematologists — physicians and scientists — share many similarities with journalists. We use facts every day to guide decision-making about patients and to hematologists — physicians and scientists — share many similarities with journalists. We use facts every day to guide decision-making about patients and to

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The 58th ASH Annual Meeting: While not a diamond jubilee, with every year that passes, we celebrated discoveries in hematology that translate into better lives for our patients. The Hallmark Company, in its semi-authoritative list, declares that the theme of 58th anniversary is faith and hope. In the clinic, immediately after the annual meeting, patients invariably begin probing, shortly after the obligatory small chat about the weather: “So, what I really want is the news from that big hematology meeting you were just at.” Although they might not fit in my luggage with the sports coats and bowties, every year I take my patient’s hopes with me to the meeting, looking for that next breakthrough. The other half of this theme is faith — faith that we can move the needle forward in the understanding and care of patients with hematologic disorders. Augustine of Hippo described the reward of faith as, “to see what you believe.” During this annual event, we see the results of our commitment and hard work come into view.

The Scientific Plenary Session is always a source of inspiration and this year was no exception. As covered in the ASH News Daily article “A Vector of Hope for the Future of Hemophilia,” results from a phase I/IIa study of a hemophilia B gene therapy that harnesses the FIX-Padua transgene were reported. By using the FIX-Padua transgene, there is increased FIX activity, so a lower vector dose can be used to minimize the need for immunosuppression while still obtaining therapeutic FIX levels of around 30 percent. With the exception of one subject who had two suspected joint bleeds requiring factor replacement, all other subjects stopped their prophylaxis, did not require any factor replacement, and had no breakthrough bleeding in 238 cumulative weeks of follow-up.

Sickle cell disease (SCD) was an area of great emphasis as advancements and unmet needs in this disease were thoroughly discussed during this year’s meeting. In the middle of ASH Central, right next to the collaboration rooms and selfie station, two sculptors worked a pile of amorphous beach sand into a monument, bringing to life the effort to cure this illness. The sands of time are shifting for this disease as we are now emerging from the drug desert. The SUSTAIN trial, which compared the P-selectin antibody Seli2G1 against hydroxyurea, captured headlines after its presentation at the Plenary Scientific Session. This is the first randomized controlled trial in more than a decade to demonstrate a significant reduction in SCD crises. This year’s Presidential Symposium highlighted state-of-the-art molecular pathways that have...
Cord Transplant Efficacy in Patients With MRD: The New Preferred Alternative Donor Source?

In the September 8, 2016, issue of The New England Journal of Medicine, Dr. Filippo Milano and colleagues from Fred Hutchinson Cancer Research Center reported that patients with acute leukemia and myelodysplastic syndrome who had evidence of minimal residual disease (MRD) prior to transplantation, the risk of relapse was significantly reduced in unrelated cord blood recipients relative to matched or mismatched volunteer donors.

This report carries with it all the caveats in interpretation inherent in retrospective data. While the authors carefully adjusted for clinical factors that could affect outcomes to limit bias, there may still be confounding factors that are important to discuss. That said, while perhaps not practice changing, the data are provocative and raise a number of interesting questions:

1. Since the majority of patients received two umbilical cord blood units, what if any influence did this have on the risk of relapse? Double cord blood transplantation has been associated with decreased relapse rates in acute myeloid leukemia, so this possible confounding variable cannot be ignored. Again, not all studies are in agreement on this matter, but this potential effect of cord blood transplantation may be the preferred alternative donor source for patients with evidence of MRD going into transplantation.

This report highlights the need for additional research to determine the best intervention needed to mitigate the risk of relapse. Cord blood transplantation has been associated with less chronic graft-versus-host disease and could enable nearly all patients to have an available donor. On the other hand, haploidentical transplants are being used increasingly, even in older patients, and may be simpler to perform and less expensive relative to cord blood. Which is the preferred source for patients without a matched related or unrelated donor? The Blood and Marrow Transplant Clinical Trials Network is currently addressing this question in its BMT CTN 1101 study (clinicaltrials.gov, NCT01877778) and we wholeheartedly support its importance, perhaps even more so given the recent report from Fred Hutchinson Cancer Research Center. Until those results are available, the available data seem to support the use of cord blood transplant as a reasonable first option in MRD-positive patients with acute leukemia and myelodysplastic syndrome who do not have a suitable matched sibling donor.

Jennifer N. Saultz, DO, Hematology/Oncology Fellow, The Ohio State University, Columbus, OH

Steven Devine, MD, Professor of Internal Medicine, Program Director, Blood and Marrow Transplant Program, The Ohio State University, Columbus, OH

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As we kick off 2017, I would first like to first express my gratitude for the unwavering leadership and service of Dr. Charles Abrams throughout the past year. I am honored to accept the baton from him, as ASH earns forward from a successful 2016 and into a new year filled with promise and purpose.

Speaking of purpose, one of the pillars of ASH’s mission is the commitment to serving clinicians and scientists through education. I am pleased to share just a few new pieces of ASH’s educational strategy that will begin to take shape in 2017, and I hope this will give you a sense for the dynamic and determined way in which we are approaching our education strategy and individual offerings.

First, ASH’s work in the key area of sickle cell disease (SCD) is something about which Charles has spoken repeatedly. ASH has recently approved a new SCD education strategy designed to ensure that all hematology-oncology professionals possess a level of competence that allows them to provide care to patients with SCD and to serve as a resource for other SCD caregivers. This initiative arose from the high priority ASH places on access to care for individuals with SCD, coupled with the need for hematologists with unique expertise to provide care for these patients. In 2017, ASH will offer new education resources to meet these goals including webinars, videos, and asynchronous meeting recordings. Consultative Hematology Course content on SCD; and education sessions at annual meeting. The Society is also exploring new initiatives for training of fellows in this critical area. As ASH is always seeking volunteers to get involved with planning and execution in this area, please visit www.hematology.org/scd to stay apprised, as well as learn about ASH’s current SCD clinical resources.

With new discoveries in treatment comes a renewed vigor in conquering the most challenging disease areas, such as acute myeloid leukemia (AML), using a collaborative approach. Last year, ASH and several partner organizations, including the American Society for Clinical Pathology and the Oncology Nursing Society, joined forces to begin creating independent educational programming designed to address knowledge gaps in the diagnosis and treatment of AML. An education grant from Celgene will help support these goals. For more, please see ASH’s press release on the AML MATTERS curriculum at www.hematology.org/Newsroom/Press-Releases/2016/6824.aspx, and stay tuned to The Hematologist in the coming months. Another very exciting collaborative effort involving AML that has already gained traction is our partnership with the Leukemia & Lymphoma Society to help spread the word about the Beat AML trial, a multicenter, multi-arm trial harnessing the power of genome mapping and targeted experimental drugs, to treat older, newly diagnosed patients. Visit www.lls.org/beataml for details.

Motivation for Education

ASH is committed to awareness and education on these advances by researchers, caregivers, and patients alike. Diseases such as SCD and AML need to be faced head on, and now is the time to begin to leverage some of our existing vehicles, including our meetings and digital-only content, in order to help us do so. And as our in-person meetings continue to grow and become more robust, ASH has also used the power of www.ashacademy.org and www.astondonem.org to expand the arsenal of educational content that you can use anytime, anywhere. Emerging topics that represent the future of our work, such as precision medicine, immunotherapies, and systems-based hematology, will enjoy a special place in the coming year and beyond.

As Dr. Gotlib and the Contributing Editors show us in the pages of this Year’s Best issue, we have together made many advances, with great promise of even further progress in the coming year.

It is a unique honor for me to assume the ASH presidency at this time of unprecedented scientific discoveries, with opportunities for their rapid translation into diagnosis, prognosis, treatment, and patient outcomes. I am humbled and deeply grateful for this distinction.

Sincerely,

Kenneth C. Anderson, MD

Contributing authors have declared any financial interest in a product or in potentially competing products or procedures, or ownership of the dollar amount. Any such financial interest is noted at the bottom of the article.

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Save the Date for Highlights of ASH

Get a synopsis of the top hematology research presented at the 2016 ASH Annual Meeting in San Diego, and improve your patient management and care strategies at the 2017 Highlights of ASH. Attendees will have the opportunity to evaluate their diagnostic techniques and therapeutic approaches as well as connect with top hematology experts and colleagues and discuss how new research and clinical updates can be translated into new patient care strategies. Highlights of ASH in North America will take place January 13-14, 2017, in Atlanta; January 20-21, 2017, in Chicago and Dallas; and January 27-28, 2017, in New York and Seattle. Highlights of ASH Latin America will occur April 7-8, 2017, in Punta del Este, Uruguay, and Highlights of ASH Asia-Pacific will take place March 10-12, 2017, in Hong Kong. To register, visit www.hematology.org/highlights.

New Conversations with Innovators

Two new videos of “The Hematologist: Conversations with Innovators” series are now available on YouTube featuring Drs. Jennifer R. Brown and David P. Steensma from Dana-Farber Cancer Institute and Harvard Medical School, respectively. In the first video, Dr. Steensma talks about his work on myelodysplastic syndromes, as well as his leadership of a new, multcenter clinical trial of the first targeted splicing inhibitor for myeloid malignancies. In the second video, Dr. Brown discusses novel small-molecule and antibody treatments for high-risk chronic lymphocytic leukemia. To view the whole series, visit www.hematology.org/Thehematologist/Multimedia.

The Hematologist Seeks Its Next Editor-in-Chief

ASH is in the initial stage of the selection process for the next Editor-in-Chief of The Hematologist for the term 2018 to 2020. Candidates with an MD, MD/PhD, or equivalent medical degree should have a broad and comprehensive knowledge of basic and clinical investigation in hematology as well as an appreciation of its subspecialty areas; a distinguished research and publications record; high standing among peers; and demonstrated writing, reviewing, and editing skills. To nominate a peer by the deadline of February 1, 2017, ASH members should submit the names of potential candidates, along with a brief, informal endorsement and a description of the candidate’s editorship experience. Nominations can be submitted via email to jllorens@hematology.org or mailed to ASH News and Reports c/o Juana Llorens, Managing Editor American Society of Hematology 2021 L Street, NW, Suite 900 Washington, DC 20036

New Contributing Editors for 2017

For the last three January/February issues, we’ve marked the start of the year in the pages of The Hematologist with two traditions—showcasing the most exciting hematologic breakthroughs of the previous year, and also spotlighting the passing of the torch from some of our Contributing Editors, themselves among the very best in their respective areas. In December 2016, in San Diego, we expressed our gratitude to four outgoing Contributing Editors: Drs. Theresa Coeetter, Adam Cuker, David Garcia, and Ann LaCasce, all of whom served three-year terms with The Hematologist.

We will greatly miss the passion and dedication of the University of the Witwatersrand’s Theresa Coetzer. Chairperson of the ASH International Members Committee. Her always engaging and timely Diffusion selections brought our readers current discoveries on a number of basic science topics, especially malaria and inherited hemolytic anemias. Adam Cuker from the University of Pennsylvania has brought his expertise in the areas of hemostasis and thrombosis to each issue of The Hematologist. Finally, many thanks to Ann LaCasce of Dana-Farber Cancer Institute, who in addition to being the very first podcaster for The Hematologist, helped to bolster each issue with her expertise in a broad range of malignant hematology subjects, including B-cell lymphoproliferative disorders and lymphoma with CNS involvement. With the explosive discoveries in CAR T cells and other targeted therapies for lymphomas, Ann’s steadfast contributions have been an invaluable piece of the puzzle that makes each issue of The Hematologist work so well.

To bridge the gaps left by the departures of Drs. Coeetter, Cuker, Garcia, and LaCasce, ASH’s Executive Committee unanimously approved the appointment of four new Contributing Editors: Drs. Caron Jacobson, Lori-Ann Linkins, Stephan Moll, and Andrew Roberts.

Dr. Caron Jacobson is a clinical and translational investigator in the lymphoma group at the Dana-Farber Cancer Institute. Her research centers on the investigation of new approaches to targeted therapies for mantle cell lymphoma in order to overcome resistance to BTK inhibitors. She is interested specifically in the use of inhibitors of HSP90 in this disease and in studying genetic and molecular markers of disease response and resistance to these agents. Dr. Jacobson is also heading the chimeric antigen receptor T cell (CAR T cells) program in lymphoma at Dana-Farber. She sees adult patients with both Hodgkin and non-Hodgkin lymphoma.

Dr. Lori-Ann Linkins is an associate professor of medicine (thrombosis) at McMaster University in Hamilton, Canada. She holds a master’s degree in health research methodology and is a deputy editor with the Health Information Research Unit at McMaster. Her research interests include heparin-induced thrombocytopenia and antiphospholipid syndrome. She was editor of the heparin-induced thrombocytopenia chapter in the American College of Chest Physicians’ guidelines and is currently a member of the ASH Venous Thromboembolism Guidelines, Heparin-Induced Thrombocytopenia Panel.

Dr. Stephan Moll is a hematologist and professor of medicine with the Division of Hematology/Oncology at the University of North Carolina. His clinical interest is coagulation, with a particular focus on thrombosis and anticoagulation. Dr. Moll’s research interests include clinical trials on new anticoagulants, better use of established anticoagulants, antiphospholipid antibody syndrome, and post-thrombotic syndrome. He takes a special interest in clinical-medical education of patients and health-care professionals.

Professor Andrew Roberts is the Metcalf Chair of Leukaemia Research at the University of Melbourne, a clinical hematologist at the Royal Melbourne Hospital, and Head of Clinical Translation at the Walter & Eliza Hall Institute. His major research interests are the development of new treatments for leukemia, lymphoma, and myeloma through translational and clinical research. He has been a leader in the clinical development of the novel targeted anticancer drug venetoclax, from the research laboratory, through clinical trials, to U.S. Food and Drug Administration approval.

We look forward to having Caron, Lori-Ann, Stephen, and Andrew lend their expertise and unique perspectives to the pages of The Hematologist and to our podcast conversations. ASH is at the vanguard of hematology education, research, and patient care, and is constantly evolving to bring new developments in each of these domains to a wider tent of hematologists, including our global colleagues. Through our print and multimedia platforms, our mission at The Hematologist is to inform Society members about the changing landscape of our profession with detailed but digestible articles crafted by our editorial team. Feeling the pulse of the readership is always a high priority, and we welcome your ideas for our featured departments such as Ask the Hematologist, Mini Reviews, and Profiles, as well as feedback in the form of Letters to the Editor.

Please stay in touch, and all the best for 2017.

~ Jason Gotlib, MD, MS, Editor-in-Chief

CONVERSATION STARTER

Featured content from Blood Advances, December 13, 2016, Volume 1, Issue 2

In the article “BCR-ABL1 gene rearrangement as a subclonal change in ETV6-RUNX1-positive B-cell acute lymphoblastic leukemia,” Dr. Karen A. Dun and colleagues report on a case of ETV6-RUNX1-positive B-cell acute lymphoblastic leukemia (B-ALL) that has acquired a BCR-ABL1 gene rearrangement as a subclonal change. The 19-year-old female patient presented with B symptoms, pancytopenia, and circulating blasts. The bone marrow aspirate was hypercellular and was infiltrated by an immature blast population that was confirmed as B-ALL by flow cytometry. Sequential fluorescent in situ hybridization was performed on the patient’s leukemic cells, which were shown to contain both ETV6-RUNX1 and BCR-ABL1 gene rearrangements. The majority of nuclei (85%) showed only the ETV6-RUNX1 gene rearrangement; however, an additional 10% also showed a variant BCR-ABL1 gene rearrangement, indicating the ETV6-RUNX1 gene rearrangement was the primary change.


Dr. Stephen Moll

Dr. Caron Jacobson

Dr. Lori-Ann Linkins

Dr. Caron Jacobson

Dr. Stephen Moll

Dr. Andrew Roberts
58th ASH Annual Meeting Wrap-Up

(Cant. from page 1)

hoisted SCD research to new heights, including chromatin remodeling and fetal hemoglobin modifying genes, in addition to gene therapy. The sky is the limit for the future of SCD treatment. To continue this upward momentum, the funds raised by the 2016 ASH Foundation Run/Walk this year have been earmarked to support ASH’s Sickle Cell Disease Initiative, a top priority for the Society.

Many of the questions that I get from patients in clinic revolve around genomics. Everything from, “Did I pass along this disease to my children?” to “Since this disease has a mutation, can you use that gene editing stuff to fix it?” Likewise, the genomic basis of hematologic cancers continues to be a major theme at the annual meeting. A few years back, ASH News Daily, not known for passing up a good pun, quipped, “Do These Genes Make My Cancer Look Bad?” While we are still assembling the complete picture of somatic mutations’ influence on hematologic malignancies, one of the new Friday Scientific Workshops focused on the role that germline mutations play in developing hematologic malignancies. Estimates often quoted in textbooks and talks suggest that roughly 2 to 4 percent of patients with hematologic neoplasms develop these diseases as a result of an underlying inherited predisposition. However, these numbers likely underestimate the true prevalence. This session certainly shined a light on the contribution of inherited predisposition alleles to disease susceptibility. Results of experiments using gene editing techniques were seen across the oral and poster session and were covered in a special-interest session on CRISPR. Furthermore, in the Plenary Scientific Session, we saw a newly identified inherited monogenetic disease involving SMARCD2, which uncovered its role in neutrophil maturation and prevention of leukemogenesis.

In addition to breakthroughs in understanding the biology of disease, we also saw the results of potentially practice-changing randomized controlled trials, making waves across treatment landscapes. The results of the GALLIUM study pitted the two heavyweights of treatment landscapes. The results of the GALLIUM study were changing randomized controlled trials, making waves across the oral and poster session and were covered in a special-interest session on CRISPR. Furthermore, in the Plenary Scientific Session, we saw a newly identified inherited monogenetic disease involving SMARCD2, which uncovered its role in neutrophil maturation and prevention of leukemogenesis.

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Thank you for participating in the 2016 ASH Foundation Run/Walk!

The 2016 ASH Foundation Run/Walk took place Sunday morning at the 58th ASH Annual Meeting in San Diego, along the scenic Embarcadero. This year, the ASH Foundation achieved a record-breaking number of registered participants at 1,300 and raised more than $104,500! One hundred percent of the registration fees and donations will benefit the ASH Sickle Cell Disease Initiative Fund. The official results of the race are as follows:

- Brian Ola, Top Male 5K
- Meredith Unger, Top Female 5K
- J. Blake Bartlett, Top Male 3K
- Shoshi Tessler, Top Female 3K

The team with the highest number of participants was Janssen Oncology. To see all results and to view the leaderboard, visit www.hematology.org/runwalk. ASH appreciates the generosity of all participants and donors and looks forward to next year’s run/walk, taking place December 3, 2017, in Atlanta, Georgia.

Thanks to our corporate supporters Seattle Genetics, Gilead Sciences, Inc., Freeman, Takeda Oncology, Pharmacyclics An AbbVie Company, and Genentech, Inc.

ASH Foundation Run/Walk

Thank you for participating in the 2016 ASH Foundation Run/Walk.

ASH News Daily

Dr. Gerds indicated no relevant conflicts of interest.
The Hematologist

HEADLINES FROM Washington

Congress Defers Final Decision on 2017 NIH Funding Until April, Passes 21st Century Cures Initiative

Bipartisanship is a rare sight in Washington these days, but it made an appearance in the last few days of the lame duck session of the 114th Congress with the passage of 21st Century Cures, a sweeping $6.3 billion medical research bill that passed both chambers of Congress by a wide margin and was signed by President Obama in mid-December. The bill authorized significant funding for various healthcare-related programs throughout the next 10 years, including $1.8 billion for Vice President Biden’s Cancer Moonshot and $1.5 billion for President Obama’s Precision Medicine Initiative. The Cures legislation also allows congressional appropriators to provide up to nearly $5 billion to the National Institutes of Health’s (NIH’s) overall budget over the next 10 years.

The authorization of Mr. Biden’s cancer initiative was one of the highlights in legislation. NIH has been involved with and supportive of the Cancer Moonshot since it was first announced by President Obama in January 2016. The Society submitted recommendations to be included in the Cancer Moonshot’s roadmap and ASH President Dr. Kenneth Anderson attended the Vice Presidential Cancer Moonshot Summit in June 2016. The inclusion of the moonshot into this newly passed legislation will ensure that the White House's cancer initiative survives after the Obama administration transitions out of office.

On the eve of adjourning for the year and narrowly avoiding a government shutdown in early December, Congress passed a five-month Continuing Resolution (CR) pushing off final funding decisions for fiscal year (FY) 2017 until April 28, 2017. The CR maintains funding for federal programs and agencies, including NIH, at FY 2016 levels minus an across-the-board cut of 0.19 percent for all programs. In addition to continuing funding for the base NIH budget, the CR also provides the institutes with additional Cures-related funding, including $40 million for the Precision Medicine Initiative and $300 million for the Cancer Moonshot.

ASH joined with several hundred members of the broader biomedical research community in sending letters to leaders of the U.S. House and Senate urging them to avoid another CR and enact a final spending package by the end of the 2016 calendar year. ASH’s letter stressed the need for sustained, predictable, real growth in federal support for medical research funded by NIH and noted the uncertainty posed by CRs, including NIH’s inability to issue new grants and the need to often withhold funds from existing projects.

Until a final 2017 spending deal is reached, it is important for your elected officials to continue to hear from you about the impact that unpredictable funding has on your research and the patients you treat. ASH will continue to closely monitor the FY 2017 appropriations process and will alert Grassroots Network members to contact their congressional delegation as needed to ensure that a final bill is passed with adequate increases to the NIH and other important public health programs.

Now Open: Apply for the ASH Congressional Fellowship Program

ASH is accepting applications for the new ASH Congressional Fellowship Program through January 31, 2017. This year-long opportunity will place a hematologist on Capitol Hill to work in a congressional office and help shape health-care and hematology policy. This new opportunity will be available for one ASH member starting in September 2017. The fellow will have the opportunity to attend a week-long orientation and will be able to choose a congressional office in which to work, with the aid of the American Association for the Advancement of Science (AAAS). The fellow will be paid at the GS-12 level and will receive health-care benefits from ASH. For requirements, more information, or to apply, please visit the ASH website at www.hematology.org/CongressionalFellowship.

Take Action in Support of Hematology

This year, and throughout the 115th Congress, ASH will continue its advocacy efforts on several important research and practice-related issues, such as:

- Seeking increased federal funding for research
- Responding to changes in physician reimbursement
- Ensuring access to safe and effective hematologic drugs
- Supporting legislative initiatives concerning sickle cell treatment and research

The Society needs the help of all ASH members to bring issues important to the future of hematology to the attention of the U.S. Congress, the new presidential administration, and U.S. governmental agencies. Members of the ASH Grassroots Network receive action alerts and information about issues in which they indicate interest. At times, Grassroots Network members are also invited to represent hematology in activities such as visits to Capitol Hill, with NIH leadership, with other regulatory agencies, and in visits with congressional leaders back home. Visit the ASH Advocacy Center at www.hematology.org/advocacy to participate in the Society’s advocacy campaigns and to join the ASH Grassroots Network. To read about ASH’s 2016 policy and advocacy efforts, please visit http://www.hematology.org/Advocacy/Policy-News.aspx.

The Hematologist: ASH NEWS AND REPORTS
The Year's Best in Sickle Cell Disease

MICHAEL DEBAUN, MD
Professor of Pediatrics and Medicine, Director of the Vanderbilt-Meharry Center for Excellence in SCD, Vanderbilt University Medical Center, Nashville, TN

In 2016, after completion of a landmark randomized controlled trial, a paradigm shift has occurred for primary stroke prevention in children with sickle cell anemia. The Transcranial Doppler (TCD) With Transfusions Changing to Hydroxyurea (TWiTCH) trial was a multicenter, open-label, phase III, noninferiority trial published in 2016. Eligibility for the trial included children with sickle cell disease (SCD) with abnormal TCD flow velocities (≥200 cm/s), but no severe vasculopathy based on magnetic resonance angiography (MRA) of the brain — a group defined as being at low risk for severe intracranial complications.

Participants were randomly assigned to receive hydroxyurea therapy or no treatment. The new therapy required a routine office visit of 30 minutes every two to three months, compared to a three- to six-hour visit each month. As expected in any randomized controlled trial, some limitations in the trial design have been noted; including the lack of a long-term follow-up to ensure the efficacy of hydroxyurea for stroke prevention because it's difficult to follow long-term in the trial was less than 24 months. Additionally, participants randomly assigned to receive hydroxyurea therapy had a median six-month overlap of receiving both transfusion and hydroxyurea. Further, despite common perception, the primary endpoint of the trial, TCD measurements, are not predictive of future strokes while receiving therapy. Among the participants of the Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP 2) trial, which had a mean follow-up of 2.4 years of transfusion therapy, 21 percent had TCD velocities that remained in the abnormal range (≥200 cm/s). Therefore, TCD measurements have only been proven predictive of strokes when not receiving therapy, and TCD measurements have not proven to have any predictive utility while receiving blood transfusion therapy.

Despite the inherent limitations of the TWiTCH trial, all observational studies to date have shown that hydroxyurea therapy significantly decreases TCD measurements. In pooled analysis of the data from two studies documenting TCD velocity after receiving hydroxyurea, the average drop in TCD measurement was 25 cm/s. The results of the TWiTCH trial coupled with the composite of the observational studies documenting that hydroxyurea therapy significantly lowers TCD measurements, make a strong case for the benefit of hydroxyurea therapy in lowering previously elevated TCD measurements.

With regard to treatment for primary stroke prevention, questions still remain. The trial looked at both hydroxyurea and blood transfusion therapy in children with elevated TCD measurements and without severe cerebral vasculopathy based on magnetic resonance angiography of the brain. Thus, families of such children are unsure as to whether the results are applicable to their situation. Unfortunately, while receiving blood transfusion therapy, the TCD measurement will not reveal whether the child will have an ongoing stroke risk. The inability to further stratify the subgroup of children with SCD into the high-risk and low-risk groups based on TCD values after treatment or the presence of severe intracranial vasculopathy is challenging because the incidence rate of strokes with regular blood transfusion therapy is very low (~1 event per 100 patient years). Another lingering question is the efficacy of hydroxyurea in preventing strokes in children with both elevated TCD measurements and silent strokes, the most likely to have strokes while not treated. The Silent Infarct Transfusion Exclusion study excluded children with elevated TCD measurements and silent strokes, thus not providing any information on this high-risk group. The small proportion of children with elevated TCD measurements and silent strokes (probably less than 5%), a randomized controlled trial is not likely to occur.

Ultimately, for these small groups of children with poorly defined, but definite increased initial and recurrent stroke risks, including those with hemoglobin SC disease with prior strokes, these data suggest that randomized controlled trials will not be necessary to consider because there are simply not enough data or clinical experience to make evidence-based decisions on management.

For individuals with sickle cell trait, 2016 saw the completion of a landmark study describing the risk of death and exertional rhabdomyolysis associated with sickle cell trait. After universal precautions were undertaken to prevent heat-related injury for all Army recruits during basic training, there was no increase in the rate of exertional rhabdomyolysis. In conclusion, for those with sickle cell trait, there was an increase in the risk of exertional rhabdomyolysis that was statistically significant (hazard ratio, 1.54; 95% CI, 1.12-2.12; p=0.008).

The results from Dr. D. Alan Nelson and colleagues highlights the now clear supercillious National Collegiate Athletic Association (NCAA) edict that all college football players must be screened for sickle cell trait or sign a document relieving the university and NCAA of any liability if an adverse event occurs. In light of the landmark study, there is clear evidence that after universal precautions, individuals with sickle cell trait participating in vigorous training do not have an excessive risk of death, and are at no greater risk of exertional rhabdomyolysis than those with a body mass index (BMI) greater than 30 compared with a BMI less than 25, or those using tobacco. Based on the strength of this large observational study, the hematology and public health communities now have a new challenge: determining whether preventive treatment components of the Army’s universal precaution strategy can be applied to the majority of high school and college athletes. The SCD community looks forward to the NCAA updating their well-intentioned, but misguided strategy of targeting individuals with sickle cell trait to prevent future injury.

Potentially, a new therapy will be available for the prevention of vaso-occlusive pain episodes in adults with SCD. For the first time since the U.S. Food and Drug Administration (FDA) approval of hydroxyurea therapy for prevention of pain episodes in SCD, a clinical trial has provided favorable evidence that a second agent, crizanlizumab, an antibody targeting the adhesion molecule P-selectin, may prevent pain episodes. In a double-blind, randomized, placebo-controlled phase III trial, participants who received crizanlizumab intravenously 15 times throughout the course of a year had a 45 percent decline in the rate of pain when compared to placebo participants. Participants who received placebo had a 46.3% rate of pain visits over the 15-month study. Participants who received crizanlizumab had a 5.4% rate of pain visits over the 15-month study.

Dr. DeBaun indicated no relevant conflicts of interest.

CRISPR/Cas9 Genome Editing: A New Era in Characterizing and Treating Hematologic Disease

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Prokaryotic bacteria and archaea have evolved an adaptive immune defense mechanism by which they recognize and regularly inter spaced short palindromic repeats (CRISPR) associated with a Cas9 nuclease to degrade foreign nucleic acids under the guidance of short RNA (gRNA) sequences. In two dependent steps involving self-synthesized gRNAs using CRISPR/Cas9 and a wild-type gene donor sequence is relatively inefficient since these cells are quiescent, and the HDR pathway is restricted to the S- and G2-phase of the cell cycle. To induce HDR in these cells is quiescent, and the HDR pathway is restricted to the S- and G2-phase of the cell cycle. To induce HDR in healthy adults, leading to elevated levels of HbF. This positive impact since the high rate of indel formation may disrupt 

3.0-mg/kg initial dose followed by 0.3 mg/kg weekly, 2) 3.0-mg/kg initial dose followed by 0.3 mg/kg weekly, 2) 3.0-mg/kg initial dose followed by 0.3 mg/kg weekly, 2) 3.0-mg/kg initial dose followed by 0.3 mg/kg weekly. Based on pharmacokinetic and pharmacodynamic modeling, these

patients. These include 1) harvesting of target cells, such as HSPCs, T cells, or infected pluri potent stem cells, 2) delivery of genetic material, 3) control of target gene expression, 4) detection and monitoring of off-target effects to avoid onco genetic events and to ensure safety, and 6) ethical implications of this new technology.

Dr. Coetzer indicated no relevant conflicts of interest.

CRISPR/Cas9 Genome Editing: A New Era in Characterizing and Treating Hematologic Disease

The natural history of severe hemophilia A and severe hemophilia B is characterized by frequent spontaneous bleeding into joints, leading to disabling hemophilic arthropathy. Prophylactic administration of factor concentrate ameliorates the disease course but is limited by the need for coagulation and an increased risk of bleeding. ` Treatment is less effective and even more costly in the 25 percent of patients with severe hemophilia A and in the 3 percent of patients with severe hemophilia B who form neutralizing inhibitors against factor VIII and factor IX, respectively. ` We now stand on the precipice of a revolution in hemophilia therapy that holds the promise of improved treatment options for patients with and without inhibitors.

The Hematologist: ASH NEWS AND REPORTS

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The natural history of severe hemophilia A and severe hemophilia B is characterized by frequent spontaneous bleeding into joints, leading to disabling hemophilic arthropathy. Prophylactic administration of factor concentrate ameliorates the disease course but is limited by the need for coagulation and an increased risk of bleeding. Treatment is less effective and even more costly in the 25 percent of patients with severe hemophilia A and in the 3 percent of patients with severe hemophilia B who form neutralizing inhibitors against factor VIII and factor IX, respectively. We now stand on the precipice of a revolution in hemophilia therapy that holds the promise of improved treatment options for patients with and without inhibitors.

Emicizumab (ACE-010) is a humanized bispecific antibody that mimics the cofactor activity of factor VIII by binding to and bridging activated factor IX and factor X. In a 12-week, open-label, noncomparative study in 11 patients with an inhibitor and five of seven patients without an inhibitor had no bleeds during the study. Phase III clinical trials to confirm the efficacy of emicizumab in patients with severe hemophilia A with (NCT02622321) and without inhibitors (NCT02847367) are ongoing, as is a single-arm study in children and adolescents (NCT02757617).

Other “non-factor” therapies for hemophilia in development include fituzumab, an interfering RNA molecule that inhibits

Numerous new developments using the CRISPR/Cas9 system were highlighted at the 2016 ASH Annual Meeting, reflecting the importance of this technology and the rapid expansion of the field. Treatment of β-globinopathies continued to focus on therapeutic targeting using CRISPR/Cas9 to delete a 13.6-kb genomic region containing putative intergenic HBF silencers. Other hematologic diseases investigated included γδ T-cell acute lymphoblastic leukemia, 18 Japanese patients with severe hemophilia (11 with and seven without inhibitors) were treated with subcutaneous emicizumab. (1) 1.0 mg/kg initial dose followed by 0.3 mg/kg weekly, 2) 3.0 mg/kg initial dose followed by 1.0 mg/kg weekly, and 3) 3.0 mg/kg initial dose followed by 3.0 mg/kg weekly. Based on pharmacokinetic and pharmacodynamic modeling, these dosing schemes were expected to result in coagulant activity at trough, similar to factor VIII levels of 3 percent, 10 percent, and 30 percent, respectively. Seventeen of 18 patients completed 12 weeks of treatment (one patient discontinued treatment early due to injection-site erythema). There were no serious adverse events, antibodies to emicizumab, or thrombomoduline events. Though the risk of thrombosis remains a potential concern in patients on emicizumab who require treatment with factor concentrate for breakthrough bleeding. Plasma concentrations of emicizumab increased in a dose-dependent manner and were accompanied by a reduction in the activated partial thromboplastin time and an increase in peak thrombin generation. Compared with the six months before initiation of emicizumab, the median normalized bleeding rate (ABR) during the 12-week study decreased from 32.5 to 4.4, 18.3 to 0, and 15.2 to 0 in the three dose cohorts, respectively. One of 11 patients with an inhibitor and five of seven patients without an inhibitor had no bleeds during the study. Phase III clinical trials to confirm the efficacy of emicizumab in patients with severe hemophilia A with (NCT02622321) and without inhibitors (NCT02847367) are ongoing, as is a single-arm study in children and adolescents (NCT02757617).

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Treatment of Hemophilia: On the Precipice of a Revolution

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antibody, and concumbin, a monoclonal antibody that targets tissue factor pathway inhibitor.1,11 Both agents may be administered subcutaneously and have shown promise in early phase clinical trials. Like elcucinab, a major potential advantage of these agents is their indifference to the presence of antibodies. At the same time, progress in gene therapy for hemophilia is advancing rapidly. SPK-801 is an adeno-associated viral (AAV) capsid with a transgene encoding factor IX FDau, a naturally occurring hyperfunctional factor IX variant. In seven subjects with severe hemophilia B who were infused with SPK-801 at a dose of 5 x 10^{11} vector genomes (vg/kg), mean steady-state factor IX activity at 12 weeks was 32.3 percent.6 BMN-270 is an AAV-factor VIII gene therapy for hemophilia A. Six of seven subjects infused at a dose of 6 x 10^{12} vg/kg achieved factor VIII levels in excess of 50 percent at 12 to 28 weeks of follow-up.11 No subjects developed a factor VIII inhibitor nor did any require immunosuppression, and there was significant reduction of total factor consumption.

This is an immensely exciting time in hemophilia. A loaded pipeline offers the potential for more effective and more convenient treatments and even cure. Amidst the current frenzy of investigation, it is nearly impossible to speculate how hemophilia will be treated in live to 10 years. The only thing we can be confident of is that it will be vastly different from how we treated it in 2016.

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Progress and Promise: Precision Medicine for Patients With Acute Myeloid Leukemia

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This year marked the first year of fiscal support for the U.S. Precision Medicine Initiative, with $251 million allotted to support this initiative, $70 million of which was specifically allocated to the National Cancer Institute to lead efforts in cancer genomics as part of the “Precision Medicine Initiative for Oncology.” Coincident with the announcement of this initiative, ASH launched a task force focused on precision medicine in 2015, aimed at evaluating and advancing the use of this emerging approach for malignant and nonmalignant hematologic diseases. “Precision medicine” is widely defined as the use of a patient’s molecular characteristics (at the genetic, transcriptomic, and/or proteomic level) to prevent, diagnose, and/or treat disease. Given the relative ease of access of blood and bone marrow cells, the field of hematology has historically been at the vanguard of the use of molecular characterization for clinical practice. At the same time, there are unfortunately several examples of hematologic disorders where outcomes have not improved despite decades of advances in molecular diagnostics. For example, it is widely cited that there have been no significant advances in outcome for patients with acute myeloid leukemia (AML) in 40 years, despite detailed knowledge of the cytogenetic and molecular markers that predict prognosis. Given these challenges, we present here a year-end critical appraisal of the progress and challenges in the use of personalized medicine to improve outcomes in AML.

Currently, treatment decisions for the majority of patients with AML depend on age and cytogenetic characteristics, and only occasionally on the use of a limited number of molecular alterations at diagnosis (mutations in FLT3, NPM1, and CEBPA, and possibly IDH1/2 mutations). However, there has been increasing appreciation of the molecular heterogeneity of AML and the potential utility of considering larger numbers of molecular alterations at diagnosis to refine prognosis. To this end, one of the largest studies to correlate mutations with outcome in AML was published this year1 and suggested the existence of additional molecular subgroups of AML that have not been widely appreciated in the past. Through sequencing 111 genes across 1,540 AML patients from three different German AML Study Group trials, Dr. Elli Papaemmanoul and colleagues suggested the existence of three novel molecularly defined subgroups of AML. In addition to currently defined AML subgroups, as follows:2

- AML with mutations in genes encoding chromatin and/or RNA-splicing factors: AML with TP53 mutations and/or chromosomal aneuploidy; and AML with IDH2 R172 mutations. The adverse prognosis associated with the “chromatin-spliceosome” and “RNA-splicing factors” AML subtypes may also be followed for minimal residual disease (MRD) assessment in AML. Not shown in the Circos plot is the potential utility of mutant IDH2 inhibition with the clinical compound aimed at targeting spliceosomal mutant cancers (H3B-8800) was described at the 2016 ASH Annual Meeting,3 and a phase I trial of this compound has now been initiated at multiple centers in the United States for patients with nearly any refractory myeloid malignancy (clinicaltrials.gov, NCT02891450). Finally, it has long been suspected that some of the challenges in the development of novel molecularly targeted therapies in AML has been the practice of testing novel agents as sole therapies in patients with relapsed or refractory disease. Sometimes without requirement of the molecular alteration targeted by the compound for enrollment. To this end, in 2016, the Leukemia & Lymphoma Society announced their sponsorship of a multistate, multiregional, multicarm trial for newly diagnosed AML patients aged 60 years and older — the “Beat AML Master Trial” (clinicaltrials.gov, NCT02692706). This trial will enroll newly diagnosed patients with AML and provide rapid genomic screening within one week. Based on the results, individual patients will be assigned to receive personalized therapy on one of several subsudies of the protocol. The targeted therapies included on the study currently include: Alectex’s CD200 antibody, samalizumab, Celgene’s IDH1 inhibitor, AG-221; Gilead’s Syk inhibitor, entospletinib; and Boehmberg and Ingelheim’s CD33 monoclonal antibody, BLX3858, with more arms to open and potentially include combination therapies.

With the culmination of a year’s worth of advances in understanding the molecular underpinnings of AML and its response to conventional therapy, we look forward to seeing these translate into new therapies and better outcomes for patients in the coming year. For example, given the U.S. Food and Drug Administration’s breakthrough therapy designation assigned for the FLT3 inhibitor, midostaurin, we are hopeful to see the first targeted therapy approved for AML.

Therapeutic and Diagnostic Interventions Based on Molecular Alterations in Acute Myeloid Leukemia (AML)

Circos plot illustrating common molecular alterations in de novo AML in adults between the ages of 16-60 years of age (center). Molecularly targeted therapies based on the presence of certain mutations are shown around the Circos plot and include mutant-selective IDH1/2 inhibitors and FLT3 inhibitors and potentially the use of venetoclax and decitabine for IDH1/2 mutant and TP53 mutant AML, respectively. In addition to the use of mutations as therapeutic targets, certain mutations may also be followed for minimal residual disease (MRD) assessment in AML. Not shown here are splicing factor mutations, which are more frequent in secondary AML and older patients and are being tested for selective sensitivity to spliceosome targeting agents.

Figure

Tectonic Shifts in the 2016 Treatment Landscape for Acute Lymphocytic Leukemia

Elizabeth R. Raetz, MD

The most promising treatment advances for both children and adults with acute lymphocytic leukemia (ALL) throughout the past year have resided in immunotherapeutic approaches. Results from trials investigating the antibody–drug conjugate inotuzumab and a single-agent salvage therapy for relapsed or refractory ALL, as well as rituximab in combination with conventional chemotherapy in the frontline, have demonstrated clinical benefits of these monoclonal antibodies in adults with B-lineage ALL (B-ALL).

T-cell engagement inotuzumab continues to show significant activity in both children and adults with relapsed or refractory B-ALL. Finally, there has also been continued progress in CD19-directed chimeric antigen receptor T-cell (CAR-T) therapy in relapsed or refractory B-ALL, results of a global registration trial in pediatric patients were presented at the 2016 ASH Annual Meeting.

The cure rate for adults with newly diagnosed ALL with intensive multiagent chemotherapy is 40 to 50 percent, and among patients who relapse, only about 20 to 30 percent will achieve a complete remission (CR). Monoclonal antibodies (MoAbs) targeting leukemia blast surface antigens offers the promise of unique mechanisms of action, distinct from traditional chemotherapy, with the potential to redirect active effector T-cells to target adverse effects. Inotuzumab is a CD22-directed humanized monoclonal antibody conjugated to calicheamicin, a cytotoxic antibiotic. In the pivotal INO-VATE randomized phase III trial in adult patients with relapsed or refractory B-ALL undergoing first or second salvage therapy, a striking improvement in remission rates was observed with inotuzumab as a single agent. Patients were randomized to inotuzumab delivered in fractionated cycles versus best available therapy with one of three conventional cytotoxic regimens. The response rate (complete remission or complete remission with incomplete hematologic recovery) for inotuzumab was 80.7 percent, compared with 29.4 percent (p<0.001) with conventional chemotherapy. Among the responders, rates of minimal residual disease (MRD) negativity were approximately three-fold higher in the inotuzumab group compared with the conventional chemotherapy group. Progression-free and median overall survival were also longer in the inotuzumab group. Based on this highly promising activity, the Children’s Oncology Group will be opening a phase II single-agent trial (C01A0112E) investigating inotuzumab in children and young adults with relapsed or refractory B-ALL in early 2017, and plans to continue to incorporate inotuzumab into frontline and salvage ALL treatment regimens in both children and adults are underway.

A beneficial effect for the addition of rituximab, a chimeric mAb targeting CD20, to standard chemotherapy has also been reported throughout the past year in adults with Philadelphia chromosome (Ph)-negative B-ALL with CD20 expression in more than 20 percent of leukemia cells. The Group for Research on Adult Acute Lymphoblastic Leukemia 2005/R (GRAALL2005/R) trial compared rituximab added to chemotherapy versus conventional chemotherapy alone in frontline B-ALL. Patients randomized to rituximab plus chemotherapy had a reduction in relapse rates and longer event-free survival (EFS) than those assigned to the control group (estimated two-year EFS 65% vs. 52%, respectively; p=0.04). Rituximab was also well tolerated in combination with chemotherapy, with no significant differences in remission deaths between the randomized regimens. While the benefit in EFS in the rituximab group did not translate into significantly longer overall survival at four years (61% vs. 50%, respectively; p=0.10), studies are underway to continue to optimize the incorporation of rituximab into ALL treatment regimens.

There has been continued progress in the treatment of ALL with CD19-directed T-cell-engager (BiTE) antibody that redirects cytotoxic T-cells to blasts expressing CD19. Inotuzumab was granted accelerated approval by the U.S. Food and Drug Administration (FDA) for use in patients who progressed following autologous stem cell transplantation (ASCT) and brentuximab vedotin. In NHL, cellular therapies, most notably CD19-directed chimeric antigen receptor (CAR) T-cells, demonstrated remarkable activity in refractory B-cell lymphoma (DLBCL), leading to numerous ongoing clinical trials with the hope of approval in the near future.

Point inhibitors directed at program cell death protein 1 (PD-1) and program death-ligand 1 (PD-L1) are associated with meaningful response rates and durable remissions in a subset of patients across a wide array of malignancies from melanoma to lung cancer. With the near-universal upregulation of PD-1, which encodes for PD-L1 and PD-L2 in Reed Sternberg cells, HL has proven to be the model disease for this approach.1 In patients with relapsed classical HL, whose disease recurred after ASCT and had progressed or failed to respond to brentuximab vedotin, treatment with nivolumab produced overall and complete response rates of 66 and 9 percent, respectively. pembrolizumab is associated with remarkable antitumor activity. In a study of 34 patients, 71 percent of whom had undergone ASCT, 65 percent of patients responded with 16 percent achieving a complete remission (CR). Consistent with other studies of both agents, autoimmune toxicities including hypothyroidism, diarrhea, and pneumonitis were common, but severe adverse events were rare. The activity of PD-1 inhibitors in NHL, however, appears to be less robust, though studies are underway to test the approach in biologically rational lymphoma subtypes such as primary mediastinal

The Evolution of Immunotherapy in Lymphoma

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In 2016, mature data emerged for novel immunotherapeutic approaches in both Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Given its impressive activity in relapsed and refractory HL, nivolumab was recently approved by the U.S. Food and Drug Administration (FDA) for use in patients who progressed following autologous stem cell transplantation (ASCT) and brentuximab vedotin. In NHL, cellular therapies, most notably CD19-directed chimeric antigen receptor (CAR) T-cells, demonstrated remarkable activity in refractory B-cell lymphoma (DLBCL), leading to numerous ongoing clinical trials with the hope of approval in the near future.

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Novel Insights Into Mitochondrial Regulation of Hematopoiesis

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Lifelong production of blood by hematopoietic stem and progenitor cells is regulated by a balance of self-renewal of stem cells, maintaining their limited supply throughout life, and differentiation, allowing for production of all blood lineages. At the 2016 ASH annual meeting, Dr. David Scadden, during his E. Donnall Thomas lecture, described that this coordination of blood production can be achieved by both inherent traits within hematopoietic stem cells (HSCs) themselves, or due to signals from the surrounding environment or niche. Past research has identified numerous potential epigenetic changes, transcription factor programming, and other cell stem traits that may govern their self-renewal or lineage differentiation choices at an inherent level, as well as stromal cell types, soluble factors, and spatial localization within the bone marrow that may govern stem cell intrinsic regulation of hematopoiesis. Several studies in 2016 have now added evidence that the HSC mitochondria may regulate the function of stem cells at both an intrinsic and extrinsic level.

Prior literature has demonstrated that the transcriptional co-regulator Prdm16 is expressed in HSCs and is important in maintaining their function. While investigating potential mechanisms governing the effect of Prdm16 on hematopoiesis, Dr. Larry Luchsinger and colleagues observed that HSCs without Prdm16 had fragmented mitochondria.1 Normal mitochondria function is maintained by a balance of fission and fusion events, coupled with mitophagy of damaged mitochondria.2 A shift in the balance toward fusion results in an increase in mitochondrial fragments. Along with this hypothesis, the authors found a reduction in the fusion protein mitofusin 2 in Prdm16 knockout HSCs. When they then subsequently knocked out mitofusin 2 in the hematopoietic system and used single HSC transplants in mice, the authors found that strikingly, the mitofusin 2 knockout HSCs exclusively demonstrated a myeloid-biased phenotype, whose white blood cell type HSCs maintained lymphoid potential. There has been increasing appreciation of HSC heterogeneity, with HSCs of differing hematopoietic potential. There has been increasing research has identified numerous potential epigenetic mechanisms governing the effect of HSC intrinsic and extrinsic mechanisms, perhaps regulating the HSC mitochondrial DNA and adding an organelle-based mechanism to the ongoing genetic and cellular studies exploring the coordinated regulation of hematopoiesis. Intriguingly, a Plenary Scientific Session presentation3 at the 2016 ASH Annual Meeting offered evidence that in addition to fusion, mitophagy, and fusion regulation of HSC mitochondria, HSC may actually have the ability to transfer their mitochondria to a neighboring bone marrow stromal cell through cell-cell contact reducing their intracellular reactive oxygen species levels and actually stimulating bone formation. This suggests that HSC mitochondria may regulate hematopoiesis in both HSC intrinsic and extrinsic mechanisms, perhaps revealing that HSC mitochondria can bridge the two philosophies discussed by Dr. Scadden during his E. Donnall Thomas lecture.

Surprisingly, a similar cell-to-cell transfer from HSCs to a neighboring stromal cell was previously described,4 demonstrating that cell-cell signaling from the HSC to a stromal cell instructed the stromal cell to produce more SDF-1, a positive supporting factor for HSCs. Perhaps, HSCs have the capacity to act as land-scapers, altering their surrounding environment to suit their needs. 2017 will certainly shed more light on these HSC-niche interactions.


The Hematologist: ASH NEWS AND REPORTS
The Year's Best in Myeloproliferative Neoplasms

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Last year brought multiple advances in the field of myeloproliferative neoplasms (MPNs), including novel insights in triple-negative MPNs, the molecular underpinnings of calreticulin (CALR)-mutated MPNs, new treatments for systemic mastocytosis (SM), and long-term data for patients with chronic myeloid leukemia (CML).

“Triple-negative” is no longer a term restricted to breast cancer. This term now also comes to cases negative for the driver mutations JAK2, MPL, or CALR. Triple-negative MPNs represent approximately 10 percent of individuals with primary myelofibrosis (PMF) and essential thrombocytemia (ET). Two separate studies, led by Dr. Jelena D. Milosevic Feenstra and by Dr. Xenia Cabagnols, identified alternative driver mutations in patients with triple-negative MPNs.1,2 In the multi-institutional European study led by Dr. Feenstra,1 10 percent (seven of 69 patients) of those with triple-negative ET and PMF had non-exon 10 MPL mutations, and 9 percent (five of 69 patients) had JAK2 mutations other than V617F and exon 12.1 Dr. Cabagnols and colleagues from France and Belgium similarly found alternative MPL mutations in cases of triple-negative ET by using whole-exome sequencing and next-generation sequencing data to determine whether they were using traditional laboratory methods, we are looking over variant MPL and JAK2 mutations. Therefore, a robust, targeted panel for multi-translocation-generation sequencing-based approaches is recommended. Even so, at least 80 percent of triple-negative MPNs are still without a known driver mutation.

Since the 2013 discovery of CALR mutations, further studies have provided exciting insights into the pathogenesis of CALR-mutated MPNs. A murine model of the CALR mutation induced MPL-independent thrombocytosis, with the type 1 mutation (52–base pair deletion) leading to a phenotype of myelofibrosis, splenomegaly, and osteosclerosis.1 The putative disease mechanism underpinning the pathogenesis of CALR-mutated MPNs was also uncovered in 2016. The mutated CALR protein was found to activate MPL (the thrombopoietin receptor), resulting in constitutive activation of JAK-STAT signaling.3 The binding of mutated CALR to MPL is independent of thrombopoietin, and the positive charge of the C-terminus of CALR was found to be critical for its transforming capacity. These findings have unmasked a new disease paradigm in which a mutated chaperone protein can induce cytokine activation and overt MPN disease. Another interesting discovery was the association of the CALR mutation with myeloperoxidase (MPO) deficiency. MPO deficiency was observed in 7 percent of PMF cases (six of 61 patients), and five of these six patients were homozygous CALR mutation carriers.4 Patients with homozygous CALR mutations had reduced MPO protein, but normal MPO messenger RNA levels, consistent with a posttranscriptional defect in MPO production. The investigators demonstrated in vitro that in the absence of CALR, immature MPO protein precursors undergo degradation in the proteasome.

2016 was also a standout year for the orphan disease SM. Proof-of-principle has now been demonstrated that clinical benefit can result from inhibiting KIT D816V — the mutated receptor tyrosine kinase that drives disease pathogenesis in 90 percent of SM patients. Dr. Jason Gotlib and colleagues reported on a global, single-arm, phase 1b clinical trial/KIT inhibitor in patients with advanced SM.5 Midostaurin elicited partial or complete regression of SM-related organ damage in 60 percent of patients, with most subjects showing a reduction in bone marrow mast cell burden and/or serum tryptase levels by more than 50 percent.6 In addition, the majority of patients exhibited reduction in splenomegaly and improvement in physical performance and quality of life. A trial is currently underway for patients with midostaurin in indolent SM led by Dr. Hanneke Kluijn-Nelemans in the Netherlands. Those data and the stage for evaluating a new generation of selective KIT D816 inhibitors, including BLU-285, whose preliminary phase I data were presented by Dr. Daniel Deangelio in an oral session at the 2016 ASH Annual Meeting.7,8 This has also been made in the molecular landscape of SM. Dr. Mohamad Jawhar and colleagues found that mutations in SKS2, ASXL1, or RUNX1 (S/A/R) were associated with an adverse prognostic in SM; both the S/A/R mutation profile and a reduction of the KIT D816V allele burden by less than 25 percent were associated with inferior outcomes with midostaurin treatment.9

Tyrosine kinase inhibitor (TKI) regimens and risk stratification have brought about significant improvements in CML treatment in 2016. Long-term follow-up data from the phase III ENSIGN trial showed that nilotinib resulted in earlier and higher complete response rates and lower risk of progression to accelerated disease over five years when compared with imatinib. Cardiovascular events were more common with nilotinib but were rarely associated with death.10 To reduce adverse effects of nilotinib, a phase II study was designed to alternate nilotinib with imatinib during first-line treatment. Data indicate that cardiovascular events are reduced when compared with other nilotinib studies and that this regimen would decrease costs for the patient.11 A follow-up study from the EUTOS population-based registry summarized first-line TKI treatments and outcome data from 2,904 patients with CML, and will serve as a benchmark for future therapeutic investigations.12 Dr. Preetesh Jain and colleagues followed BCR-ABL1 p210 transcript types in chronic-phase CML patients treated with first- and second-generation TKIs. The study found that patients with e1a2 (b3a2) transcripts, when compared with e1a2 (b2a2) transcripts, achieved earlier and deeper treatment responses, which are associated with improved event-free and transformation-free survival.13 New prognostic data were collected in a study that stratified chromosomal evolution in CML following treatment with TKIs. Abnormalities with favorable prognosis included triosomes 8, Y, and an extra copy of Philadelphia chromosome, whereas poor prognostic aberrations included i(17)(q10), +7/del7q, and 3q26.2 rearrangements.14

Finally, the 2016 ASH Annual Meeting provided further data on the clinical benefit of TKI therapy in chronic-phase CML patients treated with imatinib, nilotinib, or dasatinib. In patients achieving a minimum of one year of a deep molecular response (e.g., BCR-ABL1 <0.1% on the international scale), molecular relapse-free survival (MRFS) was 62 percent at five years, 56 percent at 12 months, and 52 percent at 24 months, respectively. Longer duration of imatinib therapy (optimal, a 5.8 years) prior to TKI-stopped was associated with a higher probability of MRFS. In the British DeEsCALate and Stopping Therapy with Imatinib, Nilotinib, or spoTyrCle (DESTINY) study, patients in at least stable MR3 (e.g., <0.1% on the international scale) decreased their TKI dose to half the standard dose for 12 months, followed by complete cessation. Molecular recurrence was lower in patients with stable MR4 (compared to lower than MR4), and neither progression to advanced phase nor loss of cytogenetic response was observed. The study found that reducing the TKI to half the standard dose was safe, and was associated with improvement in TKI-related side effects, indicating that some patients with stable long-term responses may be getting over-treated.

Dr. Allen and Dr. George indicated no relevant conflicts of interest.

References


BTK Inhibition Saunters to the Front of the Line in CLL

PAUL MOSS, PhD
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Much of the progress within hematology-oncology throughout the past 30 years has been “incremental” — valuable of course, and leading to highly effective therapies in disorders such as diffuse large B-cell lymphoma and acute lymphoblastic leukemia. However, these are the days of “disruption,” and ambitious companies now make the case for their drug in a direct challenge to chemoimmunotherapy. The updates from the 2016 ASH Annual Meeting show that at median follow-up of 28.6 months, there was a 92 percent response rate, and only four of 135 patients on ibrutinib have discontinued treatment due to progressive disease. An encouraging feature was the increasing complete response rate, which had risen to 18 percent by this time. Five-year follow-up on the PCYC-1102 trial also showed a 29 percent complete response rate and an outstanding five-year estimated PFS rate of 92 percent.1

Of course there are many unanswered questions at this point. Chemotherapy offers a (relatively) “short sharp shock” of treatment following which patients can stop medication, typically for many years before further treatment is needed. Indeed the potential for R2C to offer a functional “cure” for a subset of patients has been suggested. In contrast, BTK inhibitors seem to need continual daily therapy. Experience with imatinib has shown that patient compliance with even twice-daily treatment can be poor.2

After five years of clinical experience, the adverse effects of ibrutinib are now becoming clearer and include an incidence


The Hematologist: ASH NEWS AND REPORTS
The Year's Best in Myeloproliferative Neoplasms

BTK Inhibition Saunters to the Front of the Line in CLL


3. Fowler RA, Mittmann N, Geerts W, et al. Cost-effectiveness of non-heparin anticoagulants for the treatment of HIT, this paper also addresses a knowledge gap in the field and frames the importance of cost considerations in this disease that may prove relevant as other non-heparin anticoagulants emerge as potential therapeutic options in HIT.1


compared with the BAT arm, it was met in the 200 mg BID cohort (spleen reduction, 21.6% vs. 2.8%, p=0.001; symptom improvement, 32.4% vs. 15.9%, p=0.011). It is possible that the endpoint of symptom improvement may have been statistically significant if the full safety population (311 patients enrolled and evaluable for toxicity) was actually evaluated for the 54-week response assessment (221 patients), which was a function of the FDA-imposed clinical hold. When looking at the survival curves censored at the date of clinical hold, there is no difference in outcome.

What were the major hematologic and nonhematologic adverse events between the two doses of pacritinib and best available therapy? Were there any significant differences in the frequency of cardiac events or hemorrhagic events between the three arms?

Treatment-emergent anemia was seen in 28 percent, 24 percent, and 15 percent of treated patients in the pacritinib 400 mg daily, 200 mg BID, and BAT arms, respectively. It is worth noting that patients treated with pacritinib had a lower red blood cell transfusion requirement than those treated with BAT at both week 24 and week 42. The incidence of anemia was seen in 35 percent, 34 percent and 24 percent of patients, respectively. Importantly, there was no significant change in mean platelet count at 24 weeks in the pacritinib treatment arms. As expected, gastrointestinal toxicity across the three arms (due to FLT3 inhibition) in the form of nausea (39%, 32%, and 11%), vomiting (21%, 19%, and 5%), and diarrhea (97%, 48%, and 15%) was more frequent in the pacritinib arms compared with BAT, and these were mostly low grade, occurring within the first month of therapy, and easily managed. This was not a major reason for study drug discontinuation.

Cardiac events, including QTc prolongation, occurred at similar frequencies – 32%, 32%, and 28% for all grade events, and 13%, 12%, and 10% for grade 3-4 events in the 400 mg daily, 200 mg BID, and BAT arms, respectively; bleeding events of all grades occurred at similar frequencies (36%, 32%, and 41%); and grade 2-4 bleeding was common in the BAT arm (7%, 14%, and 7% respectively for QD, BD and BAT). The most common grade 4 bleeding events in the BD arm were epistaxis and postprocedural bleeding.

Given the findings of the study, what is your opinion about the unmet need(s) that pacritinib fulfills in the current treatment landscape of MF, and what are the next steps?

Thrombocytopenia is a recognized adverse prognostic clinical variable in MF. MF patients with thrombocytopenia (specifically platelet count <50 × 10^9/L) are at considerable risk for bleeding, disease progression, significant symptomatic burden, and poor survival. Ruxolitinib is approved for MF patients with a minimum platelet count of 50 × 10^9/L due to the expected myelosuppression seen with this agent. Therefore, these patients that are most in need of therapy are unable to enjoy the benefit of JAK2 inhibition due to limiting thrombocytopenia. Pacritinib can potentially fill this void and provide a therapeutic option for this subpopulation.

I believe that the PERSIST-2 data show the benefit of pacritinib 200 mg BID with a reasonable toxicity profile and minimal detrimental effect on a key count. This could be the initial approved indication, and perhaps further studies could be completed to demonstrate safety and efficacy at doses below 200 mg BID, with a goal to expand the approval for second line (and after 1) inability to tolerate ruxolitinib due to thrombocytopenia or 2) loss of initial response to ruxolitinib therapy. The full clinical hold placed on all pacritinib studies in February 2016 was due to the concern by the FDA of an increased risk of bleeding and cardiovascular events with pacritinib coupled with survival curves from PERSIST-1 that appeared to indicate worse survival in the pacritinib arm. However, closer analysis at 72-week follow up (presented by Dr. Ruben Mesa at the 2016 ASCO Annual Meeting) demonstrated that the survival curves were the same up to 24 weeks, and then there was a trend toward improved survival in the BAT arm that by imbalance, a greater proportion of pacritinib-treated patients with DIPPS high-risk features such as advanced age, leukocytosis, and circulating blast percentage. Additionally, when looking at the BAT patients who did not cross over to pacritinib (17 patients) there seemed to be a higher frequency of deaths (35%) compared to the cohort that crossed over to pacritinib. Also, attaining a spleen volume reduction of at least 20 percent correlated with improved survival with pacritinib therapy, but not with BAT. There was no significant difference in occurrence of cardiovascular events in these two arms until after 24 weeks, and reasons for death in the BAT arm were more frequently attributed to adverse events. Taken together, pacritinib offers a better benefit-risk ratio that is favorable for patients with low platelets, and attaining a spleen response may predict those patients who are most likely to derive a survival benefit for this novel agent.

Note added in press: On January 5, 2017, CTI BioPharma announced that the FDA’s full clinical hold on trials of pacritinib had been removed.

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Dr. Bob Löwenberg (Editor-in-Chief) and Dr. Nancy Berliner (Deputy Editor-in-Chief) have combined efforts to identify some of the most outstanding 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.

Dr. Robert M. Konopleva, Mayo Clinic, and Dr. Michael A. Greipp, University of Minnesota, report a comprehensive review of the role of targeted agents in multiple myeloma. The latest developments in the treatment of myeloma are discussed, including the use of immunotherapy, and the potential for personalized medicine in the management of this disease.

Dr. Daniel A. Lichtenstein and colleagues identify a recurring mutation in NDUFB11, a mitochondrial respiratory complex 1-associated protein encoded on the X chromosome, in five males with a congenital sideroblastic anemia. Their findings corroborate other evidence suggesting that sideroblastic anemia can be caused by dysfunction of the mitochondrial respiratory chain.

OCTOBER 27, 2016


Dr. Douglas B. Kuhns and colleagues describe the genetic basis for a disease that has mystified investigators for over 45 years, the lazy leukocyte syndrome. The typical symptoms of recurrent infections, stomatitis, a low neutrophil count, and impaired neutrophil motility that characterize this disorder can now be explained by gene mutations in actin-interacting protein 1.

NOVEMBER 3, 2016


Dr. Anthony R. Mato and colleagues report a retrospective study of clinical outcomes of 178 chronic lymphocytic leukemia patients who discontinued kinase inhibitor (KI) therapy withibrutinib or idelalisib. Toxicity is the leading cause of discontinuation of the therapy, but patients may have subsequent responses to an alternate KI.


OCTOBER 6, 2016


In this week’s plenary paper, Dr. Sanjay Khandelwal and colleagues demonstrate that the initiating event in patients who develop heparin-induced thrombocytopenia (HIT) is the activation of complement by heparin-PAR1 complexes and binding of the complexes to B cells via complement receptor 2 (CR2). These studies may help explain many aspects of the immune response leading to HIT.


Dr. Eduard J. Libourel and colleagues report that approximately 10 percent of patients with acute myeloid leukemia develop thrombosis between diagnosis and first consolidation. Elevation of D-dimer greatly increases the risk for thrombosis, suggesting that simple screening could identify patients at high risk for this surprisingly common complication.


This “How I Treat” article presents a comprehensive overview of genetic syndromes associated with familial predisposition to myeloid malignancy. The authors discuss key clinical and laboratory issues, addressing how to recognize and care for patients with hereditary myeloid malignancy, and offer recommendations to clinicians in the field.

NOVEMBER 10, 2016


Dr. Helen E. Speedy and colleagues identify germ line loss-of-function mutations involving the telomere shelterin complex in familial chronic lymphocytic leukemia.

NOVEMBER 24, 2016


Dr. Bruce D. Cheson and colleagues offer novel criteria for response to treatment that are crucial to many aspects of the evolving management of lymphoid malignancy.

S E P T E M B E R 2 9 , 2 0 1 6


This plenary paper presents the first in-depth paired analysis that compares leukemic stem cell frequencies and their genomic instability in acute myelogenous leukemia (AML) at diagnosis and relapse. These data suggest a unique biological shift in phenotype that could explain the poor response to chemotheraphy of relapsing AML.

O C T O B E R 1 3 , 2016

Blasts of a Different Sort

BY JOHN H. BAIRD, MD,* JENNY HOFFMAN, MD,* AND JASON GOTLIB, MD, MS†

1. Fellow in Hematology/Oncology, Division of Hematology, Stanford Cancer Institute, Stanford, CA
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3. Professor of Medicine, Division of Hematology, Stanford Cancer Institute, Stanford, CA

The hematologist/Images

For the solution to the quiz, visit D. Systemic lupus erythematosus
C. Gray platelet syndrome
B. Osteitis fibrosa
A. Primary myelofibrosis

Figure 2, reticulin stain) is shown in the biopsy (Figure 1, hematoxylin and eosin stain; platelet count of 83 × 10^9/L). A bone marrow biopsy (Figure 1, hematoxylin and eosin stain; Figure 2, reticulin stain) is shown in the images. What is the diagnosis?

A. Primary myelofibrosis
B. Osteitis fibrosa
C. Gray platelet syndrome
D. Systemic lupus erythematosus

For the solution to the quiz, visit The Hematologist online, www.hematology.org/ Thehematologist/Images.

Put your fellow readers to the test, and send us your Image Challenge submissions! Email case descriptions and image files to the Managing Editor at jlorens@hematology.org.

LETTER TO THE EDITOR

With reference to the November/December 2016 Image Challenge, the case of the 68-year-old woman with neutrophilic leukocytes of a longstanding duration is very instructive. I am wondering if the pseudo Pelger-Huët anomaly seen in the circled neutrophils is a manifestation of chronic neutrophilic leukemia (CNL)?

— John J. Akabutu, MD, Canadian Cord Blood Registry, Edmonton, Alberta, Canada

Authors’ Reply

We appreciate your query regarding the Image Challenge. In this case of CNL, we agree that infrequent neutrophils are present with morphology resembling the acquired (or pseudo) Pelger-Huët anomaly. This morphologic feature consists of bilobed nuclei that may be connected by a thin filament of chromatin and mimics the congenital Pelger-Huët anomaly, which is an autosomal dominant inherited disorder due to mutations in the gene encoding the lamin B receptor.

The acquired Pelger-Huët anomaly may be observed in a variety of states, including myelodysplastic disorders (MDS), MDS/myeloproliferative neoplasms (MPN) (e.g., chronic myelomonocytic leukemia or atypical chronic myeloid leukemia [CML]), acute myeloid leukemia, leukemoid reactions, chemotherapy or other drug exposures, vitamin B12 or folate deficiency, myxedema, and viral infections.

One of the diagnostic criteria of World Health Organization (WHO)-defined CNL is absence of dysgranulopoiesis; in contradistinction, “prominent” dysgranulopoiesis (e.g., >10% of observed leukocytes) is considered a major feature defining atypical CML, which was absent in this case. We additionally favored a diagnosis of CNL because of the lack of myeloid immaturity, the presence of the CSF3R T618I mutation (identified in approximately 80%-90% of CNL cases, but <10% of atypical CML cases),1,2 and morphologic findings of toxic granulation and Döhle bodies in the neutrophils — recurrent findings in CNL. However, we have encountered similar cases that exist on a morphologic spectrum between CNL and atypical CML. Although some of these examples may ultimately be assigned a diagnosis of MPN-unclassifiable, or MDS/MPN-unclassifiable, the application of WHO laboratory, morphologic, and genetic criteria should provide diagnostic specificity in most cases.

— John Bard, MD, Fellow in Hematology/Oncology, Stanford University School of Medicine, Stanford Cancer Institute, Stanford, CA
— Jason Gotlib, MD, MS, Editor-in-Chief, Professor of Medicine, Stanford University School of Medicine, Stanford Cancer Institute, Stanford, CA