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ASH Diversity, Equity, and Inclusion Statement

The American Society of Hematology (ASH) is committed to building and nurturing a global hematologic community and workplace inclusive of diverse perspectives, talents, and experiences as it works toward one collective goal: helping hematologists conquer blood diseases worldwide.

The three-pronged approach to fulfilling the Society’s commitment to diversity, equity, and inclusion is:
1. Inspiring, recruiting, and supporting researchers and clinicians from diverse backgrounds to pursue and succeed in careers in hematology and related fields.
2. Involving people with diverse perspectives, talents, and experiences in leadership, volunteer, and staff positions.
3. Advocating for policies and supporting programs that aim to eliminate health disparities in the care of hematologic patients.

ASH has demonstrated a longstanding commitment to promoting diversity among the broader community of clinicians and investigators involved in the field of hematology. In 2003, ASH established the Committee on Promoting Diversity (CPD) and launched committee efforts including the ASH Minority Recruitment Initiative (MRI). Indeed, ASH’s commitment to efforts to address issues in diversity, equity, and inclusion (DEI) extend beyond the activities of the CPD. Given recent events in the United States, ASH leaders re-examined the Society’s role in addressing injustices that affect ASH members and the populations of patients who are affected by hematologic diseases. In June 2020, ASH President Dr. Stephanie Lee described the Society’s clear commitment to ongoing efforts in diversity, equity, and inclusion in a message to ASH members (https://www.hematology.org/newsroom/press-releases/2020/message-from-the-ash-president-on-diversity-equity-and-inclusion). The ASH statement on DEI (See box) engages the Society’s broad, international membership to draw from our diverse strengths and perspectives to address disparities that affect our patients with hematologic diseases.

As exciting discoveries are made, clinical and translational investigators are key drivers in the rapid translation of basic research findings to new drug approvals. However, the number of early-career scientists currently engaged in hematology research is insufficient to meet future demand. A lack of opportunities to receive formal training and early-career mentorship contribute to this deficiency. The shortage of clinical and translational research trainees is expected to produce significant lags between scientific discoveries and future clinical implementation of cancer research, which can result in significant lost opportunities in lives saved, symptoms ameliorated, and health care cost-savings. Moreover, to effectively translate these discoveries to diverse populations, diverse groups of investigators are needed.

To address the three components of the statement of DEI, ASH has engaged members to recruit and retain diverse voices in volunteer leadership and visibility opportunities and to support diverse award cohorts through mentorship, outreach, informed study section processes, and preferential scoring.

(Cont. on page 13)
President’s Column

ASH’s Global Reach

Drew Binsky is a young travel vlogger who has one professional ambition: to visit every country in the world by June 2020. As of March 2020, he had toured 191 of the 195 United Nations–designated sovereign countries. He had almost reached his goal, but the global COVID-19 pandemic halted his travel. His YouTube videos focus on each destination’s topography, demography, culture, and food, and he has logged thousands of miles in his herculean effort. His inspiring story made me wonder: Wouldn’t it be fascinating to visit every country in the world to learn about the local medical care, and in particular, the state of hematology? In fact, ASH has many global initiatives that serve as good starting points for your journey.

If you travel to Brazil, Chile, Paraguay, Peru, or Uruguay, you will learn about amazing progress of the International Consortium on Acute Promyelocytic Leukemia (IC-APL), now the International Consortium on Acute leukemia (ICAL). APL is an uncommon but highly curable subtype of acute myeloid leukemia (AML) that launched several global initiatives. Disparities in outcomes in low-resource countries prompted the ASH International Members Committee to establish IC-APL in 2004. This network of North American and European clinicians and investigators, together with colleagues in low-resource countries, implemented a standard-of-care diagnostic and therapeutic protocol for patients with newly diagnosed APL adapted to local circumstances. The objectives were to improve outcomes, establish standards in clinical and laboratory procedures, encourage participation in clinical trials, and promote scientific collaborations. While the early death rate in Brazil was historically 32 percent (Jácamo RH et al. Haematologica. 2007;92:1431-1432), with adherence to a common protocol, the early death rate has decreased to approximately 11 percent, and the overall survival increased from 50 percent to 80 percent (Rego EM et al. Blood. 2013;121:1935-1943). ICAL has now embarked on a protocol for newly diagnosed APL with oral arsenic, ATRA, and minimal chemotherapy. The consortium is also conducting a randomized trial for AML exploring postremission strategies, and as of October 2020, almost 400 patients have been recruited.

Visit one of several Caribbean countries (Bahamas, Barbados, Jamaica, Tobago, and Trinidad) and you will learn about the Children’s International Consortium on Acute Leukemia (C-ICAL). This is a clinical network developed together with the SickKids Caribbean Initiative to establish a standard-of-care treatment protocol for acute lymphoblastic leukemia, improve patient care, encourage development of clinical trials, and promote the exchange of scientific ideas.

Travel to Africa and you will be impressed with the progress made by the Consortium on Newborn Screening in Africa, which reflects the major commitment by ASH to address many issues surrounding sickle cell disease (SCD). This network was convened to demonstrate the effectiveness of newborn screening and early interventions. Participating countries include Ghana, Kenya, Liberia, Nigeria, Tanzania, Uganda, and Zambia. The goal is to screen 10,000 to 20,000 babies each year in each country and to provide babies living with SCD with the best care. Screening and treatment have started in Nigeria and Ghana.

Return to Latin America and you will be interested to learn about the Latin American Registry in Aplastic Anemia, established in 2017 with many of ASH’s partner hematology societies (Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, Paraguay, Peru, Uruguay, and Venezuela). The goal of the initiative is to develop a registry of patients with aplastic anemia, standardize therapeutic strategies, encourage clinical trials, and promote global investigation.

You can travel almost anywhere in the world and appreciate ASH’s numerous global outreach programs designed primarily for education of hematologists and related health care professionals. The Clinical Research Training Institute in Latin America is directed toward early- to mid-career hematology faculty working in Latin America to promote the design and conduct of clinical trials. ASH and the European Hematology Association (EHA) have teamed up to create the ASH-EHA Translational Research Training in Hematology program—a yearlong mentorship program for early-career investigators that begins with a weeklong intensive course teaching biostatistics, genetics, molecular biology, and clinical trial design. The International Outreach Initiative provides educational materials to hospitals and universities in low-resource countries to address local needs in hematology. The Visitor Training Program provides funding for up to 12 weeks of training for hematologists or hematology-related health care professionals to train in a specific hematology topic at the institution of an ASH member. The pandemic, this year ASH has worked closely with partner societies to identify relevant topics for the popular Highlights of ASH in Latin America, Asia Pacific, and the Mediterranean to provide online education. Highlights of ASH are themselves highlights of ASH’s global initiatives! There are international editions of Blood with various features translated into the local language (Spanish, Portuguese, Italian, Japanese, and Chinese).

We must continue to reach outward far and wide and continue to invest resources in global programs. There are many other countries in the world to visit and colleagues with whom to collaborate and learn. Drew Binsky’s videos are compelling and educational; ASH’s global initiatives are, too. We have the opportunity and responsibility to continue to extend our reach to improve the diagnosis and treatment of patients, thereby fulfilling our mission to conquer blood disorders worldwide.

Martin S. Tallman, MD
Sometimes it’s hard to fathom that regular transitions happen even with all this chaos. But of course they do, and that includes the yearly change in our Editorial Board roster. With the ASH annual meeting being virtual, we were not able to gather and express in person the Society’s gratitude to our three outgoing Contributing Editors—Dr. Annette Kim, Dr. Teache, and Irene Gobrial. Over their three-year tenures, each brought unique expertise to the position. Dr. Kim, of the Brigham and Women’s pathology department, wrote on many of the newest aspects of molecular diagnosis and diagnostics and participated in podcasts that helped readers and listeners learn more about these developments. From the Children’s Hospital of Philadelphia, Dr. Teachey’s pediatric perspective also made its way into the pages of The Hematologist—in particular, showing how clinical research was working on testing de-escalation of care for some populations. Finally, Dr. Gobrial’s illuminating writing on myeloma corresponded with three years of incredible change in that disease. A professor of medicine at Dana-Farber Cancer Institute, Dr. Gobrial shared her notably informative insights into precursor syndromes and the role of immunotherapy.

This publication could not happen without the dedication and commitment of our Contributing Editors. Of course, with each farewell, there is always a “hello,” and I have passed on the thanks of ASH and our readership to each of these professionals and to learn from their work, expertise, and experience, and the great joys of this work is being able to interact with so many varied individuals. Of course, with each farewell, there is always a “hello,” and we are thrilled to welcome three new Contributing Editors—Drs. Robert Hasserjian, Sarah Tasian, and Saad Usmani.

Dr. Robert P. Hasserjian is a hematopathologist and professor of pathology at Massachusetts General Hospital and Harvard Medical School in Boston. His clinical interests are in diagnosis of myeloid and lymphoid neoplasia, and his research interests focus on advancing the diagnosis and clinically relevant classification of myeloid neoplasms, particularly myelodysplastic syndromes and acute myeloid leukemia. Dr. Hasserjian is the director of the Hematopathology Fellowship at Massachusetts General Hospital and is committed to hematopathology education.

Dr. Sarah Tasian is a pediatric oncologist at the Children’s Hospital of Philadelphia and University of Pennsylvania School of Medicine, with clinical and scientific interests in precision medicine therapies for high-risk childhood acute lymphoblastic leukemia and acute myeloid leukemia. Her bench-to-bedside translational laboratory research program focuses on preclinical testing of kinase inhibitors and chimeric antigen receptor T-cell immunotherapies. She also leads or co-leads several national and international early-phase clinical trials investigating molecularly targeted therapeutics in children with high-risk leukemias.

Dr. Saad Usmani is a clinical professor of medicine, the Division Chief of Plasma Cell Disorders, and Director of Clinical Research in Hematologic Malignancies at the Levine Cancer Institute/Atrium Health in Charlotte. He is an internationally recognized clinical and translational researcher focused on multiple myeloma, and in particular, high-risk multiple myeloma. In his spare time, he enjoys participating in endurance events to help raise funds for various causes.

The Hematologist Board of Contributing Editors Welcomes Three New Additions in 2021

Updated COVID-19 FAQs for Hematologists

Find regularly updated resources and responses to frequently asked questions (FAQs) by visiting www.hematology.org/COVID-19. The FAQs cover COVID-19 treatments and prevention, clinical laboratory topics, and resources from other societies. The latest FAQs provide updates on COVID-19 vaccines for patients undergoing hematopoietic cell transplantation and chimeric antigen receptor T-cell therapy (a joint FAQ with the American Society for Transplantation and Cellular Therapy); coagulopathy; acute myeloid leukemia; venous thromboembolism/anticoagulation; and other malignant, nonmalignant, and treatment-related topics. Visit www.hematology.org/covid-19FAQ for more details and to read the FAQs.

Register for the 2021 Highlights of ASH®

The 2021 Highlights of ASH® series will be an all-virtual experience that will give attendees a synopsis of the top hematology research presented at the 2020 ASH Annual Meeting, while providing networking opportunities and lessons on improving patient treatment and care strategies. Meeting registration includes access to curated content derived from all four regions where this series historically takes place: North America, the Mediterranean, Asia-Pacific, and Latin America. The platform is now open through April 2. Pre-recorded content and live experiences (with CME/MOC credits awarded) will be available to registrants for program information and to register, visit www.hematology.org/highlights.

New Clinical Practice Guidelines Now Available

In partnership with the International Society on Thrombosis and Haemostasis, the National Hemophilia Foundation, and the World Federation of Hemophilia, ASH has developed clinical practice guidelines on the diagnosis and management of von Willebrand disease (vWD), the world’s most common inherited bleeding disorder. The guidelines were published on January 12 in Blood Advances (https://ashpublications.org/bloodadvances/pages/vwd-guidelines). For more information about the guideline process and to access additional clinical and educational resources, visit www.hematology.org/vWdguidelines.

The ASH Guidelines on Use of Anticoagulation in Patients With COVID-19 were published on February 8 in Blood Advances (ashpublications.org/bloodadvances/article/11/3/872/475154). These guidelines cover the use of anticoagulation in critically and acutely ill patients with COVID-19. For more information and additional resources, visit www.hematology.org/COVIDGuidelines.

Dr. James Cook

James D. Cook, MD, an esteemed teacher and mentor, passed away in November 2020. His research focused on iron disorders, including the laboratory assessment of iron status, causes of nutritional iron deficiency, and design of international strategies for eliminating nutritional anemia worldwide. Read more in the February 2021 Society Pages of ASH Clinical News (www.ashclinicalnews.org).
Practical Issues in Lymphoma Care During the COVID-19 Pandemic

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THE CASE
A 66-year-old woman with stage IV follicular lymphoma (FL) on observation since 2017 calls to report an uncomfortable mass in her left axilla. She has no fevers, sweats, or weight loss. At the time of her call, there is a moderate but increasing level of COVID-19 in your area. The reproductive (R) value is 1.1, and COVID-19 hospitalizations are increasing. The local health care system is not overwhelmed, and the hospital-based cancer clinic where you work has been able to maintain access to diagnostic tests and treatments. The patient expresses reluctance to come into the hospital due to a fear of COVID-19.

QUESTIONS
What is this patient's risk of dying from COVID-19?

RESPONSE
An individual patient's risk of dying from COVID-19 is impacted by their risk of exposure to the virus, the nature of their exposure (prolonged, masked vs. unmasked, etc.), and their individual risk of infection and serious sequelae. At the time of writing, it is not known whether having a hematologic malignancy independently increases the risk of contracting COVID-19. We do know that patients with hematologic malignancy have a higher risk of COVID-19 mortality than patients without hematologic malignancy. A cohort study of over 17 million Britons reported that patients diagnosed with a hematologic malignancy in the previous year had a higher risk of dying from COVID-19 (adjusted HR 2.86) compared to those without hematologic malignancy.11 A meta-analysis of patients with COVID-19 and hematologic malignancy found a risk of death of 34 percent in a mainly hospitalized sample.12

There are important limitations to reports of high COVID-19 mortality in patients with blood cancer. First, many published reports of COVID-19 in patients with blood cancer are heavily enriched with hospitalized patients14; thus, mortality risk estimates may not be accurate for all-comers. Second, most published reports of COVID-19 in patients with blood cancer are based on data from early in the pandemic, and COVID-19 outcomes are improving.13 Third, while the attributable COVID-19 mortality risk from hematologic malignancy is substantial, it is much lower than the impact of advanced age (adjusted HR for age over 80 years, 20.6, compared to age of 50-59).14 A validated COVID-19 mortality risk predictor is available, incorporating regional COVID-19 risks with a patient’s demographics and comorbidities (https://COVID-19risktools.com:8443/riskcalculator). However, factors such as protective behaviors, disease-specific information, and the impact of systemic cancer treatment are beyond the scope of this calculator.

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QUESTION
Should this patient be vaccinated against COVID-19 if available?

RESPONSE
There are limited data on the safety and efficacy of the COVID-19 vaccines in patients with hematologic malignancy. However, safety data from other non-live vaccines are reassuring, and based on these data, it seems unlikely that unique safety concerns will arise for our population. However, the existing vaccination literature does raise potential concerns about vaccine effectiveness in patients with blood cancers, particularly those receiving anti-CD20 agents.15 Anti-CD20 therapy appears to have a prolonged and powerful negative impact on vaccine responses which can last for more than a year beyond the last dose of anti-CD20.16-21 It is unknown if this negative immune response will affect COVID-19 vaccines. We also don't know if different types of COVID-19 vaccines will differ in their ability to stimulate immunity in our patient population, what vaccination schedule will be optimal, or if booster doses of vaccine will be helpful. Collaborative research in this area is urgently needed. In the absence of data, our approach is to encourage COVID-19 vaccination among our patients, and when feasible, to vaccinate before starting systemic cancer treatment. Because we anticipate impaired vaccine responses in our patients, we also encourage their caregivers and household contacts to be vaccinated against COVID-19 if possible and recommend continued infection control measures such as masking and social distancing.
Featuring content from Blood Advances, Volume 5, Issue 1

**Overcoming Resistance to Targeted Therapies in Chronic Lymphocytic Leukemia**

Insight into the critical role of B-cell receptor signaling for the pathogenesis of chronic lymphocytic leukemia (CLL) led to the development of targeted therapies directed at key regulators of cell survival. Agents targeting B-cell lymphoma-2 protein, Bruton’s tyrosine kinase (BTK), and phosphatidylinositol 3-kinase are approved for treatment of CLL and have significantly improved the disease management. Nevertheless, acquired resistance to the targeted therapies is a challenge still to be resolved. The mechanisms underlying resistance are becoming clearer and include secondary mutations within the drug target and activation of bypass pathways. This knowledge has allowed development of strategies to prevent and overcome treatment resistance. Approaches to prevent resistance include targeting bypass mechanisms by combination therapies, temporally sequencing of therapies, improved clinical trial designs, and real-time monitoring of patient response. A rational design of drug sequencing may secure effective treatment options at the relapsed setting. Next-generation inhibitors and bispecific antibodies have the potential to overcome resistance to the BTK inhibitor ibrutinib. Immunotherapy, including chimeric antigen receptor-modified T-cell therapy, is explored for relapsed CLL. Here, recent advances that have contributed to the understanding of resistance to targeted therapies in CLL are discussed. Strategies for managing resistance are reviewed, including translational, real-world, and clinical perspectives. More available at ashppublications.org/bloodadvances.

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Update on the NIH Cure Sickle Cell Initiative

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Editor’s Note: At the time this issue went to press, it was announced that the initial sponsor bluebird bio, Inc., had temporarily suspended its phase III and phase III LentiGlobin® gene therapy studies to investigate two cases of myeloid malignancy that have arisen in treated patients.

Rationale for Gene Therapy
For many years, the only U.S. Food and Drug Administration-approved drug for sickle cell disease (SCD) was hydroxyurea, which leads to increases in fetal hemoglobin and subsequently retards HbS-induced sickling of red blood cells (RBCs). This effect, along with hydroxyurea-induced reduction of circulating leukocytes and other anti-inflammatory effects, are associated with decreased prevalence of vaso-occlusive crises, acute chest syndrome, stroke, and death. Other recently approved drugs that target the sequelae of HbS polymerization include L-glutamine, voxelotor, and crizanlutamib. These drugs target pathophysiologic processes downstream of the HbS point mutation and have varying and limited clinical impact. Thus, a curative option that would significantly impact the pathophysiology of HbS is desirable, and several approaches are currently being evaluated. This article aims to meet the practice hematologist’s need for information about the current development of curative therapies, to help them inform their patients and answer their questions about the pros and cons of curative therapy for SCD.

A Brief History of the Development of Curative Therapies
Allogeneic hematopoietic stem cell (HSC) transplantation using sibling donors is currently the only standard curative option for SCD. However, a related HLA-matched stem cell donor is found in only less than 20 percent of patients. Graft failure and transplant-related mortality remain challenges, and moreover, because of the inherent risk of graft-versus-host disease (GVHD), allogeneic transplant recipients often require prolonged immunosuppression.

Gene therapy, which involves genetic modification of the patient’s autologous HSCs, could potentially serve as an attractive alternative to allogeneic transplantation. The concept of gene therapy, specifically the introduction of new genes to treat blood diseases, goes back to the 1970s. Since that time, modern molecular biology tools have developed the ability to clone human genes as complementary DNA (cDNA), and to generate therapeutic gene transfer vehicles (e.g., vectors derived first from bacteria and subsequently from viruses) that can introduce cloned genes into mammalian cells. Throughout the past 20 to 30 years, viral backbones have undergone many modifications to enable in vivo gene delivery, and lentiviral vectors because of their increased ability to integrate into the patient’s HSC by either a nonviral or viral delivery vehicle. A phase I trial utilizing this editing technology to target the BCL11A enhancer region also shows promising efficacy and safety, albeit after limited follow-up thus far.3

The Basics of Gene Therapy As a Medical Procedure
HSC transplantation of either autologous HSC or gene-modified autologous HSC is conducted according to a carefully planned multistep protocol. The pretransplant regimen includes multiple measures such as HSC mobilization and procurement, RBC exchange transfusion, and marrow ablation. These steps pose significant challenges due to the inflammatory aspects of SCD. Procurement of adequate numbers of HSC is critical for the in vivo gene modification process but also likely impacts HSC engraftment efficiency. HSC procurement for transplantation in this age group has yielded inconsistent numbers of viable HSC and can trigger SCD-related morbidities such as acute chest syndrome in some patients. This practice has been mostly replaced by HSC mobilization to the peripheral blood and collection by apheresis. Granulocyte colony-stimulating factor has been widely used as an effective mobilizing agent in patients with malignancy undergoing transplantation. However, this drug is contraindicated in SCD, as it can trigger severe anemia events. The CXCR4 antagonist plerixafor is a more recently developed mobilizing agent that is well tolerated and effective in healthy autologous stem cell donors and has been used successfully in the current gene therapy trials for SCD. However, the degree of mobilization in patients with SCD is often suboptimal, as are the yields of purification by apheresis. As a result, patients may require multiple mobilization-apheresis interventions. Most gene therapy protocols have implemented RBC exchange transfusions as a pretransplant preparative regimen to prevent the occurrence of SCD-related morbidities associated with the HSC mobilization-apheresis procedure. Prior to infusion of the gene-modified HSC, myelotoxic cytotoxic therapy is administered to “make room” for the autologous transplant. Thus, analogous to autologous stem cell transplantation for malignant disorders, patients undergoing gene therapy require in-hospital monitoring of infections and blood transfusion support during the marrow recovery period. The long-term risks of genotoxic conditioning regimens include infertility and occurrence of secondary malignancy. Other potential long-term risks relate to engraftment durability as well as the potential for off-target effects of either vectors and/or editing components. Multiple working groups and committees of the National Institutes of Health (NIH) Cure Sickle Cell Initiative (www.curesickle.org) have been established to address these pre- and post-transplant issues (Table).

Another strategy involves introduction of a gene encoding a short hairpin RNA that silences the BCL11A transcription factor, which is critical for switching off HbF production after birth. Therefore, HbF production in RBCs is reactivated. This strategy is attractive because high levels of erythrocyte HbF in patients with SCD are associated with reduced morbidity and mortality. Highly encouraging results of a phase I study involving six patients suggest that this also is a promising approach for HbF induction in patients with SCD.3

The ability to alter or edit specific regions of the patient’s own genomic DNA using the CRISPR-Cas9 nuclease system is another attractive novel gene therapy approach currently being applied in gene therapy trials for thalassemia and SCD. Here, the nuclease and guide RNA are introduced into the patient’s HSC by either a nonviral or viral delivery vehicle. A phase I trial utilizing this editing technology to target the BCL11A enhancer region also shows promising efficacy and safety, albeit after limited follow-up thus far.3

Table. Cure SCD Initiative Resources and Contacts

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<thead>
<tr>
<th>Resource</th>
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<td>Sickle Cell Disease for Health Professionals (National Heart, Lung, and Blood Institute [NHBLI])</td>
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<td>NHBLI Center for Health Information</td>
<td><a href="mailto:nhlbiinfo@nhlbi.nih.gov">nhlbiinfo@nhlbi.nih.gov</a> or 1-877-NHBLI4U (1-877-645-2448)</td>
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<td>ASH Sickle Cell Disease Initiative</td>
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Although patients and clinicians may choose gene therapy to stop the relentless recurrence of pain episodes, many patients will arrive to gene therapy with significant prior damage to the brain, heart, lungs, or kidneys. Such underlying damage may worsen during the physiological stresses of the bone marrow conditioning regimen and recovery periods, and we do not know at this time what damage, if any, will be reversible once predominantly normalized red cells are circulating. Thus, gene therapy, even when successful, may not be the “cure” the patient expects.

Additionally, most gene therapy schemes do not result in production of red cells with predominantly hemoglobin A. For the most part, they result in production of cells containing both an anti-sickling Hb (e.g., AT87Q, HBF) as well as HbS. We do not yet know exactly how normally these cells will behave in the circulation. It is unclear to what extent progressive organ damage might occur after gene therapy and whether such progression will be related to specific measurable results of gene therapy such as percent HbF.

Role of the NIH Cure Sickle Cell Initiative

In 2017, NIH Director Francis Collins formed the Cure Sickle Cell Initiative to accelerate all aspects of the progress of curative therapies to the bedside. The initiative encompasses a programmatic effort to support all aspects of development of curative therapies. Another important role of the initiative is to support growth in the understanding of gene therapy and its broader implications for patients, family members, caregivers, and the public. Thus, the initiative is engaging members of those groups, soliciting their input, and using a variety of means to better understand lay patient, and family knowledge and attitudes, with the aim of having these individuals involved in the whole process of program building and clinical trial design. Among the questions being asked are, “What should the definition of a ‘cure’ be?” Additionally, the initiative is supporting economic analyses of the many costs of SCD to the health care system, to the affected individual, and to society, with and without curative therapy. Mental health implications of gene therapy clinical trial participation will also be examined.

The Sickle Cell Initiative is also supporting the development of resources for clinical trial enrollment, such as universal standardized methods of assessment of disease severity and disease intake forms to determine donor eligibility for different clinical trials (see previous article in The Hematologist).

Future Directions

There is a need to develop alternative safer, nongenotoxic (e.g., antibody mediated) approaches given the long-term sequelae of the current myeloablative conditioning regimens. Preparative regimens that target the bone marrow microenvironment either pharmacologically or via blood transfusion might lead to more efficient HSC mobilization and favor durable engraftment with a high degree of chimerism. In vivo gene therapy — the direct delivery to the patient of nucleases packaged in viral or nonviral vehicles — could be conducted on a large scale, as it obviates the need for an autologous transplant. As an alternative to gene therapy, pharmacologic HbF reactivation by small molecule regulators targeting BCL11A or other genes may have comparable impact on SCD morbidity and mortality. Although such treatment would entail long-term medication use, it is more likely to be widely implemented.


Acknowledgements

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Dr. Silberstein and Dr. Telen indicated no relevant conflicts of interest.
Expanding the Use of Rivaroxaban for Patients With Atrial Fibrillation: The RIVER Trial


ERIC TSENG, MD, MS(CH, FRCP)C

Patients with atrial fibrillation (AF) require long-term anticoagulation therapy for stroke prevention. The pivotal randomized trials in AF comparing the direct oral anticoagulants (DOACs) with vitamin K antagonists (VKAs) demonstrated a significant reduction in stroke and systemic embolism, with a reduction in major bleeding with DOACs.1 However, these trials mostly excluded patients with moderate-to-severe mitral stenosis and prosthetic heart valves. For this reason, current guidelines from the American Heart Association recommend using VKAs over DOACs for patients with moderate-to-severe mitral stenosis or mechanical heart valves.2

There remains uncertainty about the efficacy and safety of DOACs in patients with AF and bioprosthetic mitral valves. These patients were not included in the ROCKET-AF study (rivaroxaban); however, 162 such patients were included in the Aristotle (apixaban) and ENGAGE AF-TIMI 48 (edoxaban) trials.3,4 A recent meta-analysis of patients with AF and valvular heart disease aside from significant mitral stenosis and mechanical heart valves demonstrated a reduction in stroke and systemic embolism with DOACs compared with VKA. However, there is a paucity of randomized comparisons of DOACs compared with warfarin in patients with bioprosthetic valves.5 The RIVER trial provided this comparison specifically in those with AF and bioprosthesis mitral valves.

This was a randomized, open-label, noninferiority study completed at 48 sites in Brazil. Patients with AF or flutter and bioprosthetic mitral valve were randomly assigned to receive rivaroxaban 20 mg daily (or 15 mg daily if creatinine clearance is 30-49 mL/min) or warfarin (international normalized ratio target, 2.0-3.0). The primary outcome was a composite of major cardiovascular events (including transient ischemic attack, TIA, stroke, valve thrombosis, systemic embolism, or hospitalization for heart failure), death, or major bleeding at 12 months. The study included primarily younger individuals (mean age 59 years) with a mean CHA2DS2-VASc score of 2.5. Fourteen percent had prior stroke or TIA, and 35 percent had their mitral valve prosthesis implantation within one year prior to randomization.

The mean time to primary outcome was similar in the rivaroxaban and warfarin groups (3475 days vs. 3401 days; 95% CI, –1.4 to 16.3; p<0.001 for noninferiority). Death from cardiovascular causes or thromboembolic events was numerically lower in the rivaroxaban group (3.4%) compared with warfarin (5.1%), and incidence of stroke was 0.6 percent and 2.4 percent, respectively. The incidence of valve thrombosis was similar between the two groups (1.0% vs. 0.6%). Major bleeding occurred less frequently with rivaroxaban (1.4%) compared with warfarin (2.6%). In the subgroup of patients who had undergone randomization within three months of valve implantation (n = 189), the incidence of the primary outcome appeared to be numerically lower with rivaroxaban (6.4%) compared with warfarin (19.9%).

Weaknesses of this study include its open-label design, and it is unclear whether the mitral valve surgery in this younger population was done for mitral stenosis related to rheumatic heart diseases (where warfarin continues to be the recommended anticoagulant). However, this study finally provides good, randomized data supporting the use of DOACs for patients with bioprosthetic mitral valves and AF, with no differences in ischemic stroke or valve thrombosis.

Notably, these results cannot be applied to patients with other bioprosthetic valves (including aortic), or to those with mitral stenosis and mechanical valves. Indeed, other studies have demonstrated more thromboembolic complications and major bleeding when DOACs have been used in patients with mechanical valves (RE-AUGN study).6 Overall, the noninferiority of the primary outcome coupled with rivaroxaban’s superior safety profile and ease of administration suggest that this study will be practice-changing for these patients and will provide evidence for another indication for the DOACs. The RIVER and RE-AUGN studies contrast and provide an important reminder that before novel therapies are used for new indications, robust randomized studies are needed to ensure both efficacy and safety.

A Predictive Biomarker in Lymphoma: Better Late Than Never


BRAD KAHL, MD

The world of oncology has dramatically evolved in the past 25 years from reliance solely on cytotoxic chemotherapy, to the introduction of molecularly targeted agents, to the current immuno-oncology wave. Along the way, many cancer types have seen the introduction of agents whose activity is highly dependent upon some predictive biomarker. However, for lymphoma, the progress has lagged. There are examples of prognostic biomarkers (activated B-cell vs. germinal center B-cell in diffuse large B-cell lymphoma [DLBCL], double-hit status in DLBCL, p53 in mantle cell lymphoma), but nothing to tell us that patient X should get drug Y. Well, that appears to be changing, at least in follicular lymphoma (FL), with the U.S. Food and Drug Administration (FDA) approval of tazemetostat, an oral small molecule inhibitor of EZH2. The role of EZH2 in normal B-cell biology is depicted in Figure 1.

A phase II study testing tazemetostat in relapsed and refractory FL was recently published. Tazemetostat, administered at a dose of 800 mg orally twice daily, was tested in 99 patients, 45 of whom had a mutated EZH2 gene and 44 with wild-type EZH2. Treatment was administered continuously in 28-day cycles until disease progression. The adverse effect profile seemed remarkably mild. There was a low incidence of cytopenias, and gastrointestinal toxicity was distinctly uncommon. Treatment discontinuations owing to adverse events occurred in 5 percent of patients. The overall response rate was 69 percent in EZH2-mutated patients and 35 percent in EZH2 wild-type patients. The waterfall plots are depicted in Figure 2. The median response duration was 11 months in EZH2-mutated patients and 13 months in EZH2 wild-type patients.

So, what are the implications of these data and this new agent? In 2021, most patients with FL needing frontline treatment will receive some form of immunotherapy (bendamustine-rituximab, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]; obinutuzumab-CHOP). For patients relapsing after first-line immunotherapy, the best data belong to the lenalidomide-rituximab regimen, which is probably the second-line therapy of choice, although the data only apply to patients who are rituximab sensitive. For patients who are rituximab refractory, the PI3 kinase inhibitors have been an option but the safety profile for this class of agents has limited their usefulness. Tazemetostat seems to be an option preferable to PI3 kinase inhibitors, given the safety profile, and particularly if the patient has a mutated EZH2 gene. This test is available on several commercially available mutation panels and can be performed on archived formalin-fixed paraffin embedded tissue. However, establishing the mutational status is not mandatory. The FDA approval is broad – there is no requirement for the mutation and the waterfall plot (Figure 2) shows many unmutated patients can still derive benefit. Why this agent should work at all in the EZH2 wild-type patient is unclear, and more work should be done to clarify which wild-type patients are most likely to benefit. What I am saying here is we need another biomarker!

Dr. Kahl indicated no relevant conflicts of interest.

Tazemetostat seems to be an option preferable to PI3 kinase inhibitors, given the safety profile, and particularly if the patient has a mutated EZH2 gene.
Assessing the Gravity of Direct Oral Anticoagulants in Pregnancy


The safety and efficacy of direct oral anticoagulants (DOacs) is not well characterized in pregnancy, as published randomized controlled trials have excluded pregnant women. Aspirin, dabigatran etexilate, rivaroxaban, and edoxaban are all considered to have unknown or unproven safety during human pregnancies and are known to cross the placenta.4–6 Arixtra is considered “Pregnancy Class B” by the US Food and Drug Administration whereas edoxaban, rivaroxaban, and dabigatran are considered “Pregnancy Class C” based on animal studies. Current recommendations for patients on a DOAC who are planning pregnancy are to transition to low-molecular-weight heparin (LMWH). For patients with unplanned pregnancy on a DOAC, the recommendation is to transition to LMWH when discovered but not to terminate the pregnancy based on concern for fetal malformations.7

In this study, Dr. Jan Beyer-Westendorf and colleagues expand on previous work8 and add significantly to our knowledge of pregnancy risk with DOAC exposure. They performed a retrospective cohort study obtaining data from multiple sources including case reports from specialists using standardized questionnaires, pharmacovigilance databases from pharmaceutical drug manufacturers, and multinational regulatory agencies. Data collected included mother’s age, indication for DOAC treatment, date of confirmed pregnancy, details of pregnancy outcome (miscarriage, and termination), smoking status at the time of pregnancy, maternal health status (child height and weight, anatomical abnormalities, and organ dysfunction). Data were reviewed by two independent physicians, and all confirmed or possibly duplicated reports were excluded. Any fetal or neonatal abnormalities were reviewed by two independent teratology experts with classification into four categories based on relation to DOAC exposure (likely, possible, unlikely, or unrelated).

A total of 1,193 pregnancies were evaluated, and after exclusion of duplicates, 614 unique pregnancies were examined (apixaban [n=50], dabigatran [n=36], edoxaban [n=23], rivaroxaban [n=505]) with exposures between February 1, 2007, and July 9, 2020. Outcomes were known in only 336 of these pregnancies, with 188 resulting in live births, 74 in miscarriages, and 74 in elective pregnancies. Most women were in their 3rd trimester and had been on non-DOAC oral anticoagulants (VTE: 94%) and the median exposure during the pregnancy was 5.3 weeks (interquartile range, 4.0–7.0). A congenital or acquired thrombophilia was present in 42 women, and 39 had experienced a prior miscarriage. Fetal abnormalities occurred in 21 (6%) of these pregnancies, of which 15 were classified as major birth defects. Adjudication of these events determined that 12 (4%) were possibly related to DOAC exposure. The authors conclude that major birth defects seem to be lower with DOACs than what has been previously reported for warfarin (7.4%-10.8%), with no specific birth defect pattern observed, and overall miscarriage rates similar to the general population.8

Despite numerous challenges and limitations in reporting of pregnancy details and outcomes, this publication provides the largest and most up-to-date information on pregnancy outcomes with DOAC exposure. While these results are largely reassuring and provide support for prior recommendations not to terminate pregnancies solely based on DOAC exposure, they should not be considered evidence of safety of DOACs in pregnancy more broadly, especially since most of these women have relatively short exposures. Because DOACs have become the preferred anticoagulant for management of VTE, and diagnosis of VTE in women of childbearing age often leads to discontinuation of oral contraceptive therapy, proper education and counseling on possible pregnancyrelated risks remains important. Lastly, when cases of DOAC exposure in pregnancy are identified, we encourage all providers to contribute to the ongoing prospective registry9 led by Dr. Sara Middeldorp and Ingred Bistervels and the International Society on Thrombosis and Haemostasis (redcap.it/issuu/?F9=RrFCM3).

Dr. Houghton and Dr. Marshall indicated no relevant conflicts of interest.

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2. While most individuals in the sample reported at least one past nonviolent traumatic experience, 68 percent reported some

3. It was surprising to find only one other report in the literature by the same group that suggested a correlation between a

4. While reported daily pain in the sample was high, with 57% of participants being pain-free only less than 150 days in the past year. The high rate of reported exposure to interpersonal violence in this SCD sample, including nearly one-third of the participants reporting past exposure to sexual abuse, underscores the need for an intentional and targeted multidisciplinary approach to both the medical and psychological needs of this vulnerable population. Regarding the patient described above who had experienced repeated interpersonal violence, she taught me to look deeper to uncover other potential etiologies for her chronic pain.

5. It makes sense to explore the role of trauma in the etiology of CP in SCD, particularly as evidence-based interventions such as trauma-informed care may ameliorate its negative consequences. The relationship between depression, anxiety, CP, and prescription opioid use has not been fully explored in adults with SCD despite the clear link between these medical problems and opioid use.

6. Dr. Julian D. Ford and colleagues conducted an elegant retrospective case control study of 50 consecutive adults with SCD to determine the relationship between exposure to IPT, CP, and opioid use. The a priori hypothesis was that there would be an association between the number of types of IPT exposure and the likelihood of both CP and opioid use in this population. They also hypothesized a similar association between the number and types of IPT exposure and the severity of depression and anxiety symptoms experienced. Lastly, they proposed that the relationship between the number of types of IPT exposure and CP and opioid use was expected to be observed independent of the effect of the severity of depression and anxiety symptoms.

7. All participants were administered standardized screening tools including the 18-item Traumatic Events Screening Inventory (TESI) to assess trauma exposure history throughout a lifetime, the nine-item Patient Health Questionnaire (PHQ-9) to identify patients meeting diagnostic criteria for major depression, and the 20-item Zung Anxiety Scale to assess self-report of anxiety symptoms. The presence of CP was elicited by response to the single question inquiring about the presence of moderate to severe pain on more than 50 percent of days in the past six months. Additional information on participant demographics and opioid use was abstracted from the medical records.

8. While there are some limitations to this study including its retrospective sequential sampling design, which may limit its broad application, the evidence suggests that the relationship between interpersonal violence exposure and chronic pain in adult sickle cell patients is significant and warrants further investigation.
Building a Model of Myelodysplastic Syndromes From the Ground Up


ROBERT P. HASSERJIAN, MD

The diagnosis and classification of myelodysplastic syndromes (MDS) have undergone several iterations since their criteria were initially codified by the French-American-British Classification in 1982.1 These sequential classification systems have adapted by incorporating new data (for example, the definition of MDS with isolated del(5q)) that was recently expanded to include up to one cytogenetic abnormality in the core present for prior diagnosis systems. The current World Health Organization (WHO) classification of MDS still relies largely on morphologic parameters in establishing the disease subtypes.2 Indeed, specific dysplastic cytometric features of hematopoietic cells have been both validated and diagnostic prognostic criteria in MDS.3 However, evaluating dysplasia is inherently subjective and is frequently congruent with the patient’s actual cytopenias.4 Moreover, interrogation of MDS by next-generation sequencing data in recent years has elucidated a remarkable genetic heterogeneity of MDS5; yet uncertainty remains regarding how to incorporate these new data into the current classification scheme and how the different morphologic appearances of MDS may relate to the myriad mutation patterns.

Dr. Yasunobu Nagata and colleagues applied machine learning algorithms to a series of 1,097 patients with genetically characterized myeloid neoplasms. Their samples included MDS as well as some myelodyplastic/myeloproliferative neoplasms (MDS/MPN) and acute myeloid leukemia that had evolved from MDS or MDS/MPN. Rather than using existing WHO disease subtypes, they distilled the morphologic/clinical features such as blood counts) into 24 distinct individual parameters that were each scored by an experienced pathologist and correlated with specific gene mutations. They identified several significant associations between individual morphologic/cytopenia parameters and mutations, indicating that the type of dysplasia we see through the microscope is indeed a manifestation of the specific mutation profile in each unique MDS case. Unsupervised analysis based on consensus clustering revealed five patterns of co-occurring morphologic features, termed morphologic “profiles” (Figure 1, P1-P5).

Some of these profiles bore strong resemblance to well-established disease subtypes, such as MDS with excess blasts or chronic myelomonocytic leukemia (CMLML), other profiles did not correspond to any WHO disease subtype. The authors applied both unsupervised clustering techniques to create eight signatures of somatic mutations in their cohort and correlated these global signatures with the morphologic profiles. In cases lacking excess blasts termed the “low-risk” group, they found six significant morphologic-genetic profile associations that were identified in both discovery and validation cohorts (Figure 1). These included well-known associations such as the correlation of the WHO entity MDS/MPN with ring sideroblasts, and thrombocytosis (MDS/MPN-RS-T) with co-mutation of SF3B1 and Jak2. However, they also found unexpected heterogeneity and overlap in some morphologic profiles; for example, the “CMLML-like” profile included both the well-known TET2 and SRSF2 co-mutated signature, but also a signature characterized by TET2 mutation and wild-type SRSF2. Genetic signature heterogeneity was also observed in the subset of cases with excess blasts termed the “high-risk” group, which included six discrete signatures such as TP53, U2AF1, or OMNITRA mutations; significant differences in survival were found among the different genetic signatures even within these excess blast cases (Figure 2).

This work demonstrates that discrete disease subtypes indeed can be created among the heterogeneous group of MDS and related entities, by using the simple building blocks of morphologic observations, blood counts, and genetic mutation profiles, devoid of any potentially biased assumptions taken from historic classifications. Grafstream, some of these “objectively created” subtypes do overlap with current WHO classification disease entities. For example, bone marrow blast count, a cornerstone of the classification and risk stratification of all myeloid neoplasms, emerged as a critical parameter in this unbiased analysis. However, some associations, such as those defined by pancytopenia, trilineage dysplasia, and lack of any MPN features (increased megakaryocytes, fibrosis, or monocytosis) or excess blasts, do not have any clear equivalent in the WHO scheme. The closest equivalent, MDS with multilineage dysplasia, only requires bilineage dysplasia and a single cytopenia.

The term “machine learning” strikes fear into the hearts of some pathologists who worry that computer-assisted diagnosis will ultimately replace their professionally honed yet subjective interpretations of microscopic disease pathology. In fact, the work of Dr. Nagata and colleagues shows how machine learning can be a tool to perfect our classification of disease and validate the significance of morphologic findings with respect to clinically relevant disease subtypes.1 The associations they found show that MDS morphology is indeed (at least in part) an expression of the underlying genetic mutations. They identified several significant associations between individual morphologic features, with excess blasts (termed the “low-risk” group), which included six discrete morphologic subtypes, such as MDS with excess blasts or chronic myelomonocytic leukemia defined by pancytopenia, trilineage dysplasia, and lack of any MPN features (increased megakaryocytes, fibrosis, or monocytosis) or excess blasts, which do not have any clear equivalent in the WHO scheme. The closest equivalent, MDS with multilineage dysplasia, only requires bilineage dysplasia and a single cytopenia.

Validated morphologic profiles and genetic signatures in low-risk MDS. (A) Diagram depicting 8 validated morphologic and genetic associations between three of the morphologic subtypes (P2, P3, and P4) and five genetic signatures. (B) Resultant validated associations between three morphologic profiles and the genetic signatures. Adapted from Nagata Y et al. Blood. 2020;136:2249-2262.

Genetics signatures in high-risk MDS. Kaplan-Meier curves compare overall survival among patients identified by six genetic subtypes within high-risk disease; the P-value is from the log-rank test. Adapted from Nagata Y et al. Blood. 2020;136:2249-2262.


Dr. Hasserjian indicated no relevant conflicts of interest.

Clonal Hematopoiesis

(Cont. from page 1)

Lastly, the authors created a cohort of 9,437 patients (from their center and the literature6,7) with treated primary malignancies, of whom 75 developed tMN. Cause-specific Cox proportional hazards analysis showed that CH present at a VAF greater than 0.14 percent was associated with an increased MN hazard ratio, 6.8. They went on to model some potentially clinically applicable scenarios in breast cancer for discussion based on age, CH, and blood counts. Ultimately, most patients with breast cancer have a low 10-year absolute risk for MN such that deferment of adjuvant chemotherapy would not affect their absolute tMN risk. However, for women at the highest risk for the hypothesized model, adjuvant chemotherapy increased the absolute risk of tMN by approximately 9 percent, exceeding the predicted absolute benefit in overall survival of chemotherapy in many women with early-stage breast cancer.

Understanding that risk factors such as CH predispose patients to MN can help tailor individualized therapy to maximize antitumor efficacy and minimize the risks of MN. Well-designed studies such as that of Dr. Bolton and colleagues can aid in our discussions with patients, such as the decisions at the time one embarks on a course of therapy, or expectation management following therapy for cytopenias and future MN risk. Soon we may see implementation of clinical strategies at diagnosis, or further investigations of the CH seen in solid tumor biopsies.8 There remains a role for standardization of what genetic should be included in CH panels and which VAF is clinically relevant in CH.9

More recently, research has focused on minimizing alkylating therapies in breast, lung, and myeloma therapy to avoid toxicity such as MN.10-12 While the investigators of some of these treatment algorithms that incorporate novel molecular agents or immunotherapies. Finally, we recognize that the hypothesized model, adjuvant chemotherapy does not automatically lead to progression to tMN. Further studies are needed to elucidate what other factors may shift the balance toward genomic instability and clonal expansion to MN. This will ensure we provide an opportunity to identify patients at risk of MN for prevention strategies, but that we also do not short-change the therapy for the cancer we know they already have.

10. DeZern indicated no relevant conflicts of interest.

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ASH's Diversity, Equity, and Inclusion Efforts

The ASH MRI (https://www.hematology.org/awards/minority-recruitment) is one example of a successful ASH effort to increase diversity in the Society and throughout the field of hematology. Since 2003, ASH has disbursed more than $12 million across 360 awards to support underrepresented minority trainees engaging in research opportunities in hematology. ASH began the MRI with the Minority Medical Student Award Program (MMSAP), which offers introductory and continued mentored biomedical research experience to minority medical students, and the Minority Graduate Student Abstract Achievement Award (MGSSAA). Efforts were eventually extended to include support through the Minority Resident Hematology Award Program (MRHIP), Minority Hematology Fellow Award (MHFA), Minority Hematology Graduate Award (MHGA), and the ASH-Harold Amos Medical Faculty Development Program (ASH-AMFDP).

The Figure displays the connections between components of the ASH MRI. Together these programs provide a continuum of training opportunities that have been demonstrated to support and enhance the pipeline of minority physicians and investigators in hematology and in medicine more broadly. Dr. Melody Smith, a translational researcher and faculty member at Memorial Sloan Kettering Cancer Center who focuses on cellular therapy approaches for hematologic cancers, is a shining example of the impact of the ASH MRI pipeline. Dr. Smith began her research career through the MMSAP in 2006, continued training through the ASH/European Haematology Association Translational Research Training in Hematology (TRTH) program, and currently receives support for her research and career development through the ASH AMFDP award (2018-present).

The ASH CDP oversees all aspects of the MMSAP, MGSSAA, MRHIP, MHFA, and MHGA, including the selection of applicants for participation, mentor identification, and program evaluation; they also coordinate the ASH- AMFDP — a partnership between ASH and the Robert Wood Johnson Foundation. All MRI programs are built upon establishing a structured mentorship relationship. Having an experienced professional as a mentor can inspire trainees to pursue careers in hematology, encourage the mentee to seek out leadership roles, and is associated with greater career satisfaction.1 Studies show that fostering such relationships is also beneficial to the mentors, influencing academic productivity and career advancement.2,3 The ASH CDP also constructed the MRI Programs Subcommittee to support matching prospective applicants with potential mentors and supports the ASH Ambassador Program at 23 institutions. The Ambassador program promotes ASH’s career development and training programs to facilitate recruitment and retention of under-represented minority trainees to hematology and engage them in other opportunities available through ASH. The CDP also provides feedback in the development of ASH programs and educational opportunities to promote DEI at the annual meeting, and sponsors the MRI Career Development Luncheon and the Promoting Minorities in Hematology event held during the ASH annual meeting to provide minority hematologists and trainees with networking opportunities.

In 2017, the ASH Awards Committee and the Committee on Promoting Diversity created an Honorific Award to honor hematologists who have demonstrated extraordinary commitment to diversity and inclusion. The ASH Award for Leadership in Promoting Diversity (www.hematology.org/awards/honorific/leadership-in-promoting-diversity) acknowledges individuals who have provided significant leadership and mentorship in the career development of trainees from under-represented groups and whose efforts have led to a more diverse and inclusive hematologic workforce. Prominent ASH members who have received the ASH Award for Leadership in Promoting Diversity include Drs. Edward J. Benz, Jr. (2020), Griffin Rodgers (2019), Cape Johnson and José López (2018), and Betty Pace (2017). However, nominees do not have to be ASH members.

ASH continues to embrace the values of diversity and inclusion by developing new initiatives. For example, the 2020 ASH Annual Meeting included content focused on the impact of bias and racism on science, health care careers, and patient outcomes. In support of this organizational priority, ASH recently completed group listening sessions hosted by the CDP to understand broader issues of diversity and inclusion relevant to ASH members from a multitude of racial/ethnic, gender, ability, and LGBTQ+ communities. These sessions create a safe space for ASH members to share their personal and collective experiences and will enable the Society to expand the reach and impact of its DEI activities.

ASH efforts also have focused on eliminating health disparities for patients with hematologic diseases. The ASH Sickle Cell Disease Initiative (https://www.hematology.org/advocacy/sickle-cell-disease-initiative) seeks to transform outcomes for individuals globally. The ASH Research Collaborative supports metrics, measurement, and research focused on diversity and equity. We anticipate that these ASH programs will have significant impact on the improvement of outcomes in the diverse patient populations we serve.

Although we are exceptionally proud of ASH’s efforts so far, we must and will do more. Future activities will build on these prior successes. Ongoing ASH initiatives include developing a DEI toolkit for hematology training and education; continuing to recruit, engage, and expand opportunities for trainees in the ASH MRI pipelines; reinforcing efforts to overcome disparities in outcomes for underserved populations; and extending opportunities for under-represented minority hematologists in ASH leadership roles across the Society. We look forward to engaging a broad range of ASH members in these activities for the advancement of our Society and for improving outcomes for the patients we serve.


Dr. Flowers and Dr. Donald indicated no relevant conflicts of interest.
Pursuing a Chemotherapy-free Regimen in Philadelphia Chromosome-Positive ALL

**STUDY TITLE:** A Phase III, Randomized Trial of Steroids and Tyrosine Kinase Inhibitor Induction with Chemotherapy or Blinatumomab for Newly Diagnosed BCR-ABL-positive Acute Lymphoblastic Leukemia in Adults (EA1891)

**ACCRUAL GOAL:** 330 patients to be randomized over six years

**PARTICIPATING CENTERS:** All ECOG-ACRIN sites (head organization) and National Clinical Trials Network (NCTN) organizations: Alliance for Clinical Trials in Oncology, Southwest Oncology Group (SWOG), Canadian Cancer Trials Group, and HNCOG. The study is open at both academic centers as well as at larger community oncology practices in the United States.

**STUDY DESIGN:** EA1891 is a randomized, phase III international clinical trial designed to examine the efficacy of combining a tyrosine kinase inhibitor (TKI) with blinatumomab or with the chemotherapy backbone of alternating hyperfractionated cyclophosphamide, doxorubicin, vincristine, and dasmethanone (hyper-CVAD) with high-dose cytarabine and methotrexate as the initial treatment for adult patients (age 18-75 years) with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL).

Patients receive a prephase treatment with glucocorticoids and TKI for one- to three-week period. The specific TKI (either dasatinib or ponatinib) can be selected by the treating physician. Patients are then randomized to induction therapy with TKI and two cycles of blinatumomab with central nervous system prophylaxis or TKI and four cycles of the hyper-CVAD chemotherapy backbone. Minimal residual disease (MRD) analysis will be performed at week 15 following induction therapy (end of cycle 2 for blinatumomab) in patients with + for 4 cycles at the induction-consolidation period (TKI arm). The BCR-ABL1 transcript level will be determined by quantitative reverse-transcription polymerase chain reaction, and a level of at least 0.01 percent must be achieved to be considered a molecular remission. Patients who achieve an MRD-negative remission may proceed to allogeneic hematopoietic stem cell transplantation (HSCT) or continue with defined protocol consolidation and maintenance therapy based on the treating investigator’s discretion. Patients with MRD-positive remissions following induction therapy will be offered crossover to the alternate discretion. Patients with MRD-positive remissions following induction therapy will be offered crossover to the alternate discretion. Patients with MRD-positive remissions following induction therapy will be offered crossover to the alternate discretion.

The primary endpoint of the study is to compare overall survival (OS) in patients with newly diagnosed Ph+ ALL randomized to receive induction-consolidation therapy with TKI, glucocorticoids, and blinatumomab versus a chemotherapy and TKI combination induction-consolidation therapy. Secondary endpoints include the end-of-induction MRD response rates (week 15 of therapy), event-free survival, and the toxicities of the blinatumomab arm as compared to the chemotherapy arm. Another key secondary endpoint will observe the outcome of patients who proceeded to allogeneic HSCT after treatment with blinatumomab and TKI and allogeneic HSCT after treatment with blinatumomab and TKI.

**RATIONAL:** Ph+ ALL is characterized as a high-risk subtype due to the substantial risk of relapse. The major breakthrough in this disease that has improved patient survival, and the toxicities of the blinatumomab arm as compared to the chemotherapy arm. Another key secondary endpoint will observe the outcome of patients who proceeded to allogeneic HSCT after treatment with blinatumomab and TKI and allogeneic HSCT after treatment with blinatumomab and TKI.

The question for the field now is whether intensive cytoytic chemotherapy is required to achieve the best rates of CMR or whether novel immunotherapy such as blinatumomab can achieve equivalent or improved rates of CMR with less toxicity, thus improving outcomes for all patients with Ph+ ALL and obviating the need for cytoytic chemotherapy: EA1891 is primed to address this important clinical question.

**COMMENT:** Due to the relative rarity of Ph+ ALL (it accounts for approximately 25% of adult cases of ALL), there are few randomized control trials in this disease. Most clinical trials that have informed the treatment of Ph+ ALL have been single-arm phase II studies. Thus, additional related questions remain as to the comparative oncologic and allogeneic utility of allogeneic HSCT. Myeloblastic allogeneic HSCT has represented the only curative option in the pre-TKI era.16,17 In the TKI era it has been a mainstay of treatment for younger patients with suitable donors, but several studies that suggest survival benefit.18,19 With the introduction of more potent TKIs (such as ponatinib) or novel immunotherapy (such as blinatumomab), one critical question is to be answered: can HSCT benefit patients who meet and maintain CMR. Unfortunately, this question cannot definitively be answered by EA1891, as the sample size for a randomized comparison was prohibitive. It is likely, however, that a significant number of patients will be referred for transplant in this study, and investigators can collect descriptive data about the outcomes of patients who undergo transplantation and those who do not on the two arms of the study. Also of interest is whether there will be less transplant-related mortality in patients who received a chemotherapy-free induction and consolidation regimen followed by allogeneic HSCT. Finally, this trial may also provide significant information as to whether a chemotherapy-free approach can offer a long-term cure for older patients, unfit patients, or patients who are unwilling to undergo an allogeneic HSCT. The hope is the addition of the combination of a potent TKI and effective immunotherapy to the current frontline regimen will further improve CMR and eliminate the need for chemotherapy and/or allogeneic transplantation.

Rallying Macrophages in the Fight Against MDS and AML

STUDY TITLE: A Phase 1b trial of Magrolimab Monotherapy or Magrolimab in Combination With Azacitidine in Participants With Hematological Malignancies

CLINICALTRIALS.GOV IDENTIFIER: NCT03248479

SPONSOR: Gilead Sciences

PARTICIPATING CENTERS: 26 study locations across the United States and one in the United Kingdom

ACCRUAL GOAL: 287 participants

STUDY DESIGN: This is a phase lb study to evaluate the effects of magrolimab, a first-in-class anti-CD47 antibody in myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). This study began accrual in 2017 and was designed as a nonrandomized, open-label trial comparing magrolimab both as monotherapy and in combination with azacitidine. The regimen uses a priming dose for magrolimab and subsequent escalation titrated in Philadelphia chromosome-positive acute myeloid leukemia—results of the prospective multicenter LALA-04 trial. Blood Adv. 2016;1:250-259.


RESULTS TO DATE: The results to date seem promising, particularly in high-risk populations such as patients with TP53-mutant AML. The MDS patient data were reported at the European Hematology Association conference in 2020, with 91 percent of evaluable patients with MDS showing evidence of an objective response and 42 percent of patients achieving CR. The CR figure rose to 56 percent after six months of therapy indicating the response is both durable and typically deepens over time. Combination therapy was otherwise generally well tolerated. An update was also presented at the 2020 ASH Annual Meeting for the AML cohort on the trial with evidence of an ORR of 63 percent and CR rate of 42 percent. Importantly, with a purposeful bias for selecting patients with TP53-mutant disease, ORR and CR rates were comparable at 69 percent and 45 percent, respectively, with a median OS of 12.9 months—a significant improvement compared to the azacitidine/venetoclax combination for TP53-mutant AML (~5-7 mo. OS).

COMMENT: This study represents the first in-human trial of macrophage immune checkpoint therapy to be used in the context of myeloid malignancies, specifically in MDS and AML, correlating with the analogous use of T-cell immune checkpoint therapies in lymphoid and solid organ cancers. To date, immunotherapy approaches in AML have been somewhat disappointing, with only CD33 targeting with gemtuzumab ozogamicin in AML receiving FDA approval. The significance of the magrolimab results to date is reflected in the FDA’s decision to grant Breakthrough Therapy designation in the U.S. as of September 2020.

Immunotherapy approaches in AML have been somewhat disappointing, with only CD33 targeting with gemtuzumab ozogamicin in AML receiving FDA approval. The significance of the magrolimab results to date is reflected in the FDA’s decision to grant Breakthrough Therapy designation in the U.S. as of September 2020.

RATIONALE: CD47 expression on a cell function as a macrophage immune checkpoint—presenting an antiphagocytic or “don’t eat me” signal by way of its interaction with the signal regulatory protein α (SIRPα) receptor on macrophages. Importantly, CD47 expression appears to be upregulated on cancer cells including leukemia stem cells, providing a potential basis by which magrolimab may be of benefit (Figure). Preclinical studies support that reactivation of this pathway is particularly relevant in the contexts of AML1 and lymphoid malignancy15 with additional work suggesting that synergy between azacitidine and magrolimab is possible,16 thus forming the basis of the current trial. The potential for a novel therapy with an alternate mechanism of activity being added to the current limited armamentarium for therapies for MDS has certainly attracted significant attention. The reduced efficacy of other combinations, such as azacitidine and venetoclax in the context of TP53-mutant disease, also highlights an area of unmet need in the realm of myeloid malignancies.

RESULTS TO DATE: The results to date seem promising, particularly in high-risk populations such as patients with TP53-mutant AML. The MDS patient data were reported at the European Hematology Association conference in 2020, with 91 percent of evaluable patients with MDS showing evidence of an objective response and 42 percent of patients achieving CR. The CR figure rose to 56 percent after six months of therapy indicating the response is both durable and typically deepens over time. Combination therapy was otherwise generally well tolerated. An update was also presented at the 2020 ASH Annual Meeting for the AML cohort on the trial with evidence of an ORR of 63 percent and CR rate of 42 percent. Importantly, with a purposeful bias for selecting patients with TP53-mutant disease, ORR and CR rates were comparable at 69 percent and 45 percent, respectively, with a median OS of 12.9 months—a significant improvement compared to the azacitidine/venetoclax combination for TP53-mutant AML (~5-7 mo. OS).

COMMENT: This study represents the first in-human trial of macrophage immune checkpoint therapy to be used in the context of myeloid malignancies, specifically in MDS and AML, correlating with the analogous use of T-cell immune checkpoint therapies in lymphoid and solid organ cancers. To date, immunotherapy approaches in AML have been somewhat disappointing, with only CD33 targeting with gemtuzumab ozogamicin in AML receiving FDA approval. The significance of the magrolimab results to date is reflected in the FDA’s decision to grant Breakthrough Therapy designation in the U.S. as of September 2020.

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**January 14, 2021**


The mechanisms that regulate specific histone marks and consequent transcriptional repression are critical for hematopoietic development but poorly understood. In a Plenary Paper, Dr. Peng Xu and colleagues describe a new mechanism that drives terminal human erythroid differentiation, identifying the heterochromatin-associated protein BAHD1 as a major target of the E3 ubiquitin ligase FOXO11 and showing that degradation of BAHD1 relieves transcriptional repression. This allows GATA1-mediated activation of many erythroid genes.


The diverse clinical presentations of systemic mastocytosis (SM) reflect neoplastic mast cell (MC)–related mediator release and organ damage, but the most severe mediator symptoms are often found in patients with indolent SM, including those with minimal MC burden. Dr. Georg Greiner and colleagues shine new light on this conundrum by revealing that hereditary alpha tropismia occurs in high prevalence among patients with SM associated with an increased risk of severe mediator-related symptoms.

**January 28, 2021**


The C5 inhibitor eculizumab has opened the door to therapeutic blockade of the terminal complement pathway in practice and raised questions about its regulation. In a Plenary Paper, Dr. Marco Mannes and colleagues describe potentially paradigm-shifting research related to the complement cascade with important translational implications for complement-driven diseases such as paroxysmal nocturnal hemoglobinuria, atypical hemolytic-uremic syndrome, and antiphospholipid syndromes.


Dr. Laurene Fenwarth and colleagues tackled the challenge of how to choose which patients should be selected for allogeneic hematopoietic stem cell transplant in first remission. By incorporating genomic data via the “knowledge bank” of Dr. Moritz Gerstung and colleagues, minimal residual disease data, and the existing standard recommendations (European LeukemiaNet 2017), they demonstrate enhanced predictive power for benefit and for harm in a cohort of 656 patients prospectively enrolled in a French national trial.

**February 11, 2021**


Plasma exchange and immunosuppression have been the standard treatment for acquired immune thrombocytopenic purpura (TTP) for the last three decades. In a study reported in this month's Blood, Dr. Paul Coppo and colleagues provide evidence that translates clinical trial data into everyday clinical practice for the potential addition of the anti-von Willebrand factor nanobody caplacizumab to that standard.


In these two short reports, the authors approach the issue of whether hydroxyurea (HU) use in young males has major irreversible effects on sperm production. Dr. Laure Joseph and colleagues analyzed and compared sperm parameters in male patients with sickle cell disease (SCD) who were exposed or not exposed to HU before puberty. They report semen abnormalities in all patients but no differences between groups. Independently, Dr. Anne-Sophie Gille and colleagues provide evidence for the lack of in vivo HU-related decreases in the spermatogenic pool in biopsy specimens from young males with SCD but evidence for a negative effect of SCD itself. Together, these reports suggest that the use of HU in young men does not adversely affect fertility.