Reducing the Likelihood of Harm Associated With Use of Anticoagulant Therapy

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To improve safe prescribing of anticoagulation, the Joint Commission published an impressive document in 2019 that contains a wealth of information on, and links to, protocols and guidelines for various anticoagulation issues, including appropriate drug selection and dosing, reversal and management of major bleeding, perioperative management, laboratory monitoring, and patient education. While this comprehensive document might initially seem difficult to navigate, it is a great resource for anyone interested and involved in establishing hospital- and systems-wide anticoagulation guidelines and quality improvement activities.

The Joint Commission has explained that this focus on anticoagulation management arose in response to an increase in adverse events (AEs) associated with anticoagulation use. In a collective investigation of emergency department visits between 2013 and 2014 for any outpatient adverse drug events, anticoagulation was responsible for 17.6 percent of visits. The most common cause of anticoagulation-associated AEs is medication errors, and the use of EPs can help improve safe prescribing of anticoagulation.

Table: Six New Elements of Performance (EPs) in the Joint Commission’s NPSG.03.05.01

<table>
<thead>
<tr>
<th>EP</th>
<th>Appropriate drug selection and dosing</th>
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<tbody>
<tr>
<td>EP 1</td>
<td>The hospital/organization uses approved protocols and evidence-based practice guidelines for the initiation and maintenance of anticoagulant therapy that address medication selection; dosing, including adjustments for age and renal or liver function; drug-drug and drug-food interactions; and other risk factors as applicable.</td>
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<thead>
<tr>
<th>EP</th>
<th>Management of bleeding</th>
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<tr>
<td>EP 2</td>
<td>The hospital/organization uses approved protocols and evidence-based practice guidelines for reversal of anticoagulation and management of bleeding events related to each anticoagulant medication.</td>
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<tr>
<th>EP</th>
<th>Perioperative management</th>
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<tr>
<td>EP 3</td>
<td>The hospital uses approved protocols and evidence-based practice guidelines for perioperative management of all patients on oral anticoagulants.</td>
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<th>EP</th>
<th>Laboratory testing</th>
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<tr>
<td>EP 4</td>
<td>The hospital/organization has a written policy addressing the need for baseline and ongoing laboratory tests to monitor and adjust anticoagulant therapy.</td>
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<tr>
<th>EP</th>
<th>Adverse event reporting, continuing quality improvement</th>
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<tr>
<td>EP 5</td>
<td>The hospital/organization addresses anticoagulation safety practices through the following: Establishing a process to identify, respond to, and report adverse drug events, including adverse drug event outcomes. Evaluating anticoagulation safety practices, taking actions to improve safety practices, and measuring the effectiveness of those actions in a time frame determined by the organization.</td>
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<tr>
<th>EP</th>
<th>Education of patients</th>
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<tr>
<td>EP 6</td>
<td>The hospital/organization provides education to patients and families specific to the anticoagulant medication prescribed, including the following: Adherence to medication dose and schedule. Importance of follow-up appointments and laboratory testing (if applicable). Potential drug-drug and drug-food interactions. The potential for adverse drug reactions.</td>
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President’s Column

Striking an Unwavering Balance

As I approach the end of my three-year term as an ASH officer and my year as ASH president, it is natural to reflect on the experience while also looking forward with great anticipation to the 61st ASH Annual Meeting in Orlando. This year promises to be truly exciting with something for everyone, including a lineup of all-star invited speakers who are the thought leaders in our discipline, and an exciting program of new science presented as posters and oral sessions. All aspects of hematology will be represented at the meeting, with talks encompassing malignant and nonmalignant diseases, basic and clinical science, and pediatric and adult conditions. Some common scientific themes running through the meeting this year will be big data analytics, artificial intelligence, precision medicine, immunology and immunotherapy, and “hemato-metabolism.” As always, practice-changing clinical and translational research will be highlighted, including during the Late-Breaking Abstracts session, and will undoubtedly create a buzz in the national media. It will be bittersweet for me personally to pass the gavel to Dr. Stephanie Lee, but I will do so with confidence that the Society will be in great hands under her leadership.

My main goals as ASH president have been to provide sound stewardship to an organization with a great mission and strategic vision, and to serve as a positive and forceful public face for the Society in our advocacy efforts and our engagement with our North American and international members. Much of this work has been in partnership with our dedicated and talented volunteer executive committee, especially the ASH officers and councilors. I am proud of all that ASH has accomplished during the past three years as we balance our commitment to growth and advancement with a steadfast focus on our shared purpose. It has been especially gratifying to see the ASH Research Collaborative make astounding progress in establishing both the Data Hub and Sickle Cell Disease Clinical Trials Network, and to see our investment in evidence-based clinical practice guidelines come to fruition in venous thrombo-embolic diseases, sickle cell disease, immune thrombocytopenia, von Willebrand disease, and acute myeloid leukemia. Most of the initial group of nearly 20 guidelines have been completed and published, or will be so in 2020.

I have been particularly interested in the hematology workforce pipeline, and I am pleased that several efforts have been launched to develop creative solutions to foster recruitment and retention of physicians and scientists in our field, including supporting a rigorous longitudinal study of hematologists in training, holding a summit on mentoring in early 2020, creating a task force focusing on early-career PhDs in hematology, and beginning conversations around novel training pathways for hematologists, such as hematology-only tracks. Simultaneously, our tireless advocacy for an evidence-based approach to maintenance of board certification in hematology seems to have gained traction, as the ABIM is finally getting in line with recommendations of experts in adult learning and with other boards within the ABMS to move away from high-stakes periodic summative exams for recertification.

As a hematologist who has devoted my clinical and academic career to hemostasis and thrombosis (HT), I encouraged ASH during my tenure as an officer to examine ways in which our Society could better engage with this core constituency. An HT working group of ASH volunteers was established nearly three years ago, and several exciting projects have been developed or are under development. This year we will again hold a special reception for the HT community at the annual meeting and also pilot a novel “poster walk” wherein hematology trainees interested in HT can participate in a curated walking tour led by recognized HT knowledge leaders, and during which six high-impact posters will be discussed. Lastly, I encourage everyone to take a look at the special “Focus on Classical Hematology” supplement to the October edition of ASH Clinical News. This edition includes an interview with me as well as more detailed information on numerous HT-related ASH activities.

It has been an honor and a pleasure to serve as ASH president in 2019. It has been one of the most meaningful experiences of my career. I look forward to seeing many of you in Orlando in December.
ASH Elects New Leadership

**VICE PRESIDENT:**  
Jane Winter, MD  
Professor of Medicine, Hematology and Oncology, Northwestern Medicine Feinberg School of Medicine, Chicago IL  
Dr. Winter will serve a one-year term as vice president, followed by successive terms as president-elect and president.

**COUNCILLORS:**  
Alison Loren, MD, MSCE  
Associate Professor of Medicine, Hospital of the University of Pennsylvania/Perelman School of Medicine, Philadelphia, PA  
Dr. Loren will serve a four-year term as councillor.  
Bob Löwenberg, MD, PhD  
Professor of Medicine, Department of Haematology, Erasmus University Rotterdam, Rotterdam, Netherlands  
Dr. Löwenberg will serve a four-year term as councillor.

FROM THE EDITOR:  
A Note on the 2020 Redesign

**LAURA C. MICHAELIS, EDITOR-IN-CHIEF, THE HEMATOLOGIST**

I sat down to write this brief editorial today with pen and paper. My goal is to introduce our readership to our print redesign – better layout, a more modern look, and clearer signposts within our articles. And yet, here I am, writing on a desk I inherited from my mother’s grandmother and thinking about the earliest printing presses and their significance.

Nearly everything I write these days is composed using a keyboard. I imagine, in fact, much of our readership have always written that way: never feeling the compulsion to pull out a pen and notebook during a meeting or sharpen a pencil before heading to a lecture. For those of us of a certain age, however, there is still a feeling of comfort in picking up a pen – the feel of the ink as it leaves the nib; the intimate tension of the metal as it scratches against the weave of the paper. Even the sound of the pen moving is familiar and resonant. These sensations remain familiar and remind me of letters written to boyfriends, of last-minute term papers, of brainstorming sessions around a table after dinner in a cafeteria, of thank you letters to grandparents long ago passed away.

And yet, one of the great things that I hope that I’ve learned from the work I do is to welcome change. So often, our therapies and approaches are woefully inadequate, so proving that the next best thing works and should replace what you do currently is something to celebrate.

So when our managing editor approached me and said that The Hematologist was getting a graphical redesign, I was optimistic and encouraged. The hope was that readers would find it easier to navigate and gentler on the eyes. Diffusion articles will be called out with special headers and will continue to lead the front page and then be clustered in the center section. We anticipate that readers will notice alterations in some of the fonts and the layout. We’ve added more white space to improve readability, and better highlighting our figures and explanatory graphics. I sincerely hope that all of you find the changes satisfying and easy-on-the-eyes. That was certainly my reaction.

Let me assure you, however, that the core purpose of The Hematologist is to provide you, the readership, with expertly curated, concisely written summaries of key developments in the science of blood and blood disorders. We want you to read this to deepen your understanding of your own field and get insights into science and clinical care that are outside of your specialty. And we want this to be a source of news about the Society itself – its current actions and future aims. While we believe adapting to change is a sign of growth, we absolutely want to keep hold of what has made this publication popular since it was started back in 2003. In short, we want to keep hold of what’s working but still continually improve and evolve.

In keeping with this spirit, let us know what you think about our new look and how we are doing with the mission. Are there topics or features you would like to see more often? Are we keeping you abreast of what’s happening with ASH? Drop us a line at TheHematologist@hematology.org, or, if you feel like it, sit down and write a letter. We would love to hear what you think. Thanks for reading.
Immune Thrombocytopenia Purpura Versus Inherited Thrombocytopenia in Adults

THE CASES

Patient 1 is a 56-year-old woman referred for preoperative evaluation of thrombocytopenia prior to cochlear implants. She was diagnosed with immune thrombocytopenia purpura (ITP) in childhood with platelet counts of 30,000 to 90,000/µL. Therapy included prednisone, intravenous immunoglobulin (IVig), splenectomy, rituximab, and azathioprine, all with minimal to no effect on her platelet count. She suffered no significant bleeding events through childbirth and surgeries (tonsillectomy, cholecystectomy, C-section, and cataract removal). She has required no red cell transfusions. The patient’s medical history was notable for systemic lupus. There was no family history of blood disorders or abnormal counts. For three weeks prior to this visit she was receiving romiplostim injections. Her platelet count was 143,000/µL. Hemoglobin, hematocrit, white blood cell (WBC) count, and differential were all normal (Figure 1).

Patient 2 is a 25-year-old woman referred for thrombocytopenia, with counts ranging from 60,000/µL to 100,000/µL. She was diagnosed with systemic lupus and was prescribed hydroxychloroquine for joint symptoms. There was no abnormal bleeding with wisdom teeth extraction. Platelet count was 63,000/µL with immature platelet fraction of 37 percent. Immature platelet fraction measures the newest, reticulated platelets and should rise with platelet production. Hemoglobin, hematocrit, WBC count, and differential were all normal. Alanine aminotransferase was elevated at 54 U/L, and alkaline phosphatase was 148 U/L (Figure 2).

THE QUESTION

What is your approach to distinguishing between inherited thrombocytopenia (IT) and ITP?

MY RESPONSE

Diagnosis of ITP is a diagnosis of exclusion. The 2011 ASH Clinical Practice Guidelines (1) state the diagnosis of ITP must meet the following criteria: a platelet count below 100,000/µL, absence of other known causes. To what extent must one go to disprove other causes? Testing for hepatitis C and HIV were specifically mentioned as advisable, and a bone marrow examination was unnecessary for “typical” ITP. Typical, however, is not defined. Most hematologists would take a thorough history for drug or toxin exposures, other comorbidities often associated with low platelets such as advanced liver disease, and those in which secondary ITP is found, including lupus, antiphospholipid syndrome, and other autoimmune diseases. Abnormalities of other cell lines make an ITP diagnosis suspect, but patients can be anemic from bleeding due to low platelets. Periperal smear examination often reveals some large platelets, but not giant ones. Treatment with standard high-dose steroids or IVIg usually produces a prompt rise in platelet count, even if not sustained.

Table

<table>
<thead>
<tr>
<th>Gene</th>
<th>Platelet Size</th>
<th>Inheritance</th>
<th>Associated Characteristics</th>
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<tbody>
<tr>
<td>CBFA2</td>
<td>Normal</td>
<td>AD</td>
<td>Myelodysplasia, AML development</td>
</tr>
<tr>
<td>RUNX1</td>
<td>Normal</td>
<td>AR</td>
<td>Monosomy 22</td>
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<tr>
<td>GATA-1</td>
<td>Large</td>
<td>X-linked</td>
<td>Dyserythropoietic anemia; thalassemia-like</td>
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<tr>
<td>GFI1B</td>
<td>Large</td>
<td>AD</td>
<td>α granule deficiency</td>
</tr>
<tr>
<td>ANKRD26</td>
<td>Normal</td>
<td>AD</td>
<td>“Gray platelet” syndrome; absent α granules, myelofibrosis evolution</td>
</tr>
<tr>
<td>NBEAL2</td>
<td>Large</td>
<td>AD/AR</td>
<td>Risk of leukemia</td>
</tr>
<tr>
<td>MYH9</td>
<td>Large</td>
<td>AD</td>
<td>Nephritis, cataracts, sensorineural hearing loss, elevated LFTs, “Döhle-like” neutrophil inclusions</td>
</tr>
<tr>
<td>ACTN1</td>
<td>Large</td>
<td>AD</td>
<td>Low reticulated platelet counts</td>
</tr>
<tr>
<td>TUBB1</td>
<td>Large</td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>CYCS</td>
<td>Normal to small</td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>GP9</td>
<td>Large</td>
<td>AD</td>
<td>Mono-allelic Bernard-Soulier</td>
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<tr>
<td>WAS</td>
<td>Small</td>
<td>X-linked</td>
<td>Wiscott-Aldrich; severe immune deficiency or thrombocytopenia only</td>
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<tr>
<th>Gene mutations outside of platelet production</th>
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<tbody>
<tr>
<td>WVF</td>
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<tr>
<td>ABCG5, ABCG8</td>
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<td>ADAMTS13</td>
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Abbreviations: AD, autosomal dominant; AR, autosomal recessive; LFTs, liver function tests; TTP, thrombotic thrombocytopenic purpura. Developed from Noris P and Picci A. (2)

Figure 1. Patient 1 peripheral smear

Figure 2. Patient 2 peripheral smear

Raised Suspicions

There are no hard and fast rules, and there will be exceptions on both sides of the diagnosis. I think twice about an ITP diagnosis versus IT if I encounter any of the following:

1. Incidental finding of low platelets with blood testing instead of a bleeding presentation
2. Very high mean platelet volume or giant platelets (as big as a red cell) on the peripheral smear
3. Platelet count greater than 30,000/µL at presentation
4. No or minimal platelet response to steroids, IVIg, or other ITP immune suppression treatments; note that some IT will respond to thrombopoietin agonists
5. “My mom has ITP, too!” or other family members with low platelets
6. Family history of myelodysplasia or leukemia; and
7. Concomitant medical problems present in known IT syndromes
A major barrier to proper diagnosis is insurance companies’ unwillingness to cover genetic testing for diagnostic purposes in adults. The panels are expensive, and the answer is usually “no.” An additional barrier is the need to identify at-risk genes. Even in cases with obvious pedigrees of low platelets, often the gene testing is negative for known mutations. Incomplete penetrance, de novo mutations, or autosomal recessive inheritance lower suspicions and thus genetic investigations.¹

The importance of the correct diagnosis was laid bare in a report of pregnancy outcomes in 181 women with proven IT. Fifty-seven or 31 percent of cases had been misdiagnosed as ITP, and 44 received unnecessary treatment, including 15 splenectomies.¹

In my own practice, I have seen hip replacements owing to avascular necrosis from chronic steroid use given for an incorrect ITP diagnosis.

### Patient Follow-up

Patient 1’s case is familiar to most hematologists as the expected clinical findings in MYH9 disorders (formerly called May-Hegglin, Fechtner’s, Epstein, or Sebastian syndromes) with a history of cataracts and sensorineural hearing loss. However, the other manifestations did not develop until later in life, thus the early erroneous diagnosis and treatment. No response to the treatment should have raised red flags about the accuracy of the diagnosis. She did not have renal insufficiency. Her MYH9 gene was sequenced and a novel mutation found. Software predicted this mutation would produce disease. Her platelet count rose with eltrombopag, and her ear surgery was accomplished safely.

The second case observes the daughter of patient 1. Patient 2 has the same MYH9 mutation. Her diagnosis was far more difficult given the lupus and possible liver disease, but her mother was known to have thrombocytopenia, which is key. She was initially misdiagnosed as ITP and encouraged to take steroids, but she wisely refused. Her mother’s MYH9 gene diagnosis came after this patient’s presentation. She does not currently have renal disease or cataracts. Her hearing is slightly decreased.


## Advocating for Hematology Doesn’t Require Getting on a Plane

To help drive change in Washington, you don’t always have to travel to Washington. Meeting with and building relationships with your senators and representatives is a powerful way to advocate on behalf of hematology from your home state. Members of Congress have local district offices that they and their staffs regularly visit, and these can be fruitful venues to meet and build working relationships with your elected officials.

The Hematologist spoke with the Vice Chair of the ASH Committee on Government Affairs, Dr. Jennifer Holter-Chakrabarty, who met with members of his Oklahoma congressional delegation during the August congressional recess. As a member of the Committee on Government Affairs, Dr. Holter-Chakrabarty helps shape the Society’s legislative policy positions by reviewing issues of import to members, working on policy statements and evaluating the most effective ways to advocate for change within Congress and in state and federal agencies.

Before joining the committee, Dr. Holter-Chakrabarty was an advocate for patient care who was known for being engaged in transplant- and hematologic malignancy-related advocacy efforts in her home state.

As an advocate, Dr. Holter-Chakrabarty has worked to speak out and build relationships with her legislators through a combination of letter writing, attending town halls, and scheduling in-person meetings. “It goes without saying that one should advocate often and with purpose,” said Dr. Holter-Chakrabarty.

With that spirit and sense of purpose, Dr. Holter-Chakrabarty arranged two important meetings to introduce herself and the field of hematology to a few members of the Oklahoma delegation. In her meeting with newly elected Representative Kendra Horn (OK-6), Dr. Holter-Chakrabarty discussed the work being done at the University of Oklahoma Health Science Center, focusing on her research in chimeric antigen receptor T-cell (CAR-T) treatment.

In another meeting, she shared information about cutting-edge hematology research with Representative Tom Cole (OK-4), the ranking member of the House Labor, Health, and Human Services Appropriations Subcommittee. That particular meeting carried special significance because the subcommittee oversees and appropriates funding for the National Institutes of Health. Meeting in person “helped me clarify to my congressional representatives how national policy affects local change and more directly, my patients,” said Dr. Holter-Chakrabarty.

Honing your message and sharing personal stories and examples are key for being a successful advocate and having an effective meeting with your legislator. “When you advocate, you must be prepared with solid data, a clear message, and personal experiences that highlight the significance of what you are advocating for,” Dr. Holter-Chakrabarty explained. “On a personal level, meeting with my legislators allowed me to thank them for policies that had a major impact on continuing my research and improving the treatment outcomes of my patients. It was also an opportunity for me to clearly identify areas where further progress could be made and barriers to success could be addressed.”

When encouraging others to get involved, Dr. Holter-Chakrabarty emphasized that legislators are listening to the opinions of their constituents. Whether it is a tweet, a letter, or a phone call, “our voices, both individually and collectively, make a difference,” she said.

There are many ways to get involved in advocacy. “ASH members should stay connected with the grassroots networking events at the annual meeting, advocacy efforts on ASH’s website, or by social media to engage their congressional members … and stay apprised of health care-related issues that affect their patients. When possible, they should engage both state and federal congressional members at their local offices,” Dr. Holter-Chakrabarty stressed.

All ASH members can participate in the Society’s advocacy work by joining the ASH Grassroots Network to receive regular updates about the Society’s advocacy efforts and information about how to contact their members of Congress. Additionally, staff in the ASH Government Relations and Practice Department are available to help set up meetings with congressional staff in Washington, DC, or in a legislator’s state or district office. ASH staff can also provide the information needed to be an effective advocate, including fact sheets and relevant talking points. For more information, visit www.hematology.org/advocacy or contact ASH Senior Manager, Legislative Advocacy, Tracy Roads at troads@hematology.org.

“Each person’s advocacy is personal,” said Dr. Holter-Chakrabarty, “but collectively, we can create important change.”

### Mark Your Calendar for Policy and Practice Lunches at the ASH Annual Meeting

The ASH Grassroots Network Lunch will be held on Saturday, December 7, from 11:15 a.m. to 12:15 p.m., in Regency Ballroom SU of the Hyatt Regency in Orlando. The lunch will provide an opportunity for ASH leaders and colleagues to discuss the potential effects to hematology from the changing political landscape in Washington and the upcoming 2020 elections. Attendees will have the opportunity to learn about ASH’s advocacy efforts, including the Society’s advocacy efforts in Congress and how to become an effective advocate for hematology. Chair of the Committee on Government Affairs, Dr. Alan Rosmarin will moderate the session.

On Sunday, December 8, from 11:15 a.m. to 12:30 p.m., ASH will host the ASH Practice Partnership (APP) Lunch, a special session dedicated to the practice community. This year’s APP Lunch will focus on genomic/genetic testing. Panelists will first highlight basic concepts in genomic/genetic testing; afterwards, the application of molecular methods in benign and malignant hematologic diseases will be discussed using a case-based approach with the aim to illustrate when tests should be ordered, how to understand and interpret the results, and what to do about them. Speakers include Drs. David Wu, Michelle P. Lambert, and Rebecca McClure. ASH Committee on Practice Chair Dr. Joseph Alvarnas will moderate the session.
Revisiting the History of Haploidentical Transplantation

AMIR STEINBERG, MD; UROOSA IBRAHIM, MD; AND LUIS ISOLA, MD
1. Associate Professor, Stem Cell Transplantation and Cellular Therapy Program, The Mount Sinai Hospital, New York, NY
2. Stem Cell Transplant and Cellular Therapy Fellow, Stem Cell Transplantation and Cellular Therapy Program, The Mount Sinai Hospital, New York, NY
3. Professor, Stem Cell Transplantation and Cellular Therapy Program, The Mount Sinai Hospital, New York, NY

The year 199 marks 50 years since Dr. William Dameshek, a pioneer in the field of hematology, passed away. As the founding editor of Blood, his accomplishments and contributions to hematology are extensive. Among other achievements, he is well-known for developing a unifying concept of myeloproliferative disorders. He was an early user of nitrogen mustard for hematologic malignancies and one of the first to incorporate its use in autologous transplantation.

Dr. Dameshek’s visionary approach to hematology, particularly in the field of transplantation, cannot be overstated. He established his career in Boston, arriving at The Mount Sinai Hospital in New York in 1966. He was directing his efforts toward the achievement of clinical bone marrow transplantation (BMT) in aplastic anemia (AA) and leukemia patients when he passed away from a stroke on October 6, 1969. Several years later, the Center for International Blood and Marrow Transplant Research (CIBMTR) contacted our program to follow up on a patient who received a stem cell transplant in 1969 under the care of Dr. Robert Taub. At the time Dr. Taub was an attending physician working closely with Dr. Dameshek. In an interview, Dr. Taub indicated that after Dr. Dameshek did his initial work on transplantation in Boston he wanted to further expand on its utility at Mount Sinai. Dr. Taub, with another young associate, Dr. Arnold Rubin, continued the efforts under Dr. Dameshek’s tutelage.

Unable to find medical records going that far back, Mount Sinai’s BMT program performed an internet search of the patient’s name and found an obituary dated 1999. Sinai’s BMT program performed an internet search of efforts under Dr. Dameshek’s tutelage. Another young associate, Dr. Arnold Rubin, continued the further expand on its utility at Mount Sinai. Dr. Taub, with his initial work on transplantation in Boston he wanted to interview, Dr. Taub indicated that after Dr. Dameshek did the encounter with Dr. Dameshek vividly, describing him as a physically impressive man.

The patient’s daughter indicated that her brother was thought to be a “better” match for her mother. She also mentioned that the transplantation was initially not successful and that the doctors had to use her cells as well, but neither Dr. Taub nor Dr. Rubin endorsed this information. Dr. Rubin recalled that the chromosome testing on the patient’s blood sample after transplantation showed a female complement. The Human Genetics Program at our institution has no cytogenetic records going that far back. The patient died in 1999, at the age of 90. Her only medical problems were osteoporosis, a hip replacement, and a shoulder injury that never quite healed. Her son-in-law recalled the patient had “low platelets” and had occasional gum bleeding. The institution where she received her end-of-life care did not have any laboratory values dating back to 1999.

In 1968, Dr. George Mathé and colleagues reported the first clinical use of pretransplant antithymocyte globulin (ATG) in a 42-year-old man with acute myeloid leukemia who received a bone marrow graft from his brother.

One month post-transplantation, there was complete restoration of hematopoiesis. The report by Dr. Taub and senior author Dr. Dameshek appears to be the first use of ATG in a nonleukemic AA patient and may also represent the first documentation of haploidentical transplantation in AA.

Author’s Note: The authors obtained consent for publication from the patient’s next of kin.


Dr. Steinberg, Dr. Ibrahim, and Dr. Isola indicated no relevant conflicts of interest.

A Skin Lesion in a Pediatric Patient: A Close Call

GABRIELA GHEORGHE, MD; AND GIRISH VENKATARAMAN, MD
1. Department of Pathology, Children’s Minnesota, Minneapolis, MN
2. Department of Pathology, The University of Chicago Medicine, Chicago, IL

A 15-year-old girl presented with a three-month history of an erythematous rash on the medial side of the left breast. This was initially diagnosed as extramedullary myeloid tumor (EMMT).

The patient received standard therapy for acute myeloid leukemia. Although bone marrow and cerebrospinal fluid analysis at the end of therapy showed no evidence of disease, there was cutaneous relapse in three months. An excisional skin biopsy was performed and showed an extensive/malignant appearing infiltrate involving dermis and underlying soft tissue and sparring epidermis and adnexal structures. Images of low- and high-power hematoxylin and eosin (H&E) (Figures 1 and 2) as well as CD4 (Figure 3) and CD123 (Figure 4) immunostains are shown. In addition to these markers, a panel of immunostains revealed the dermal infiltrate to be positive for TdT, CD3, CD43, CD45, TCL1, TCF4, and CD68 KP1 (faint, focal).

Additionally, cytogenetics showed RB1 deletion and loss of chromosome 17.

What is the diagnosis?
A. EMMT
B. Blastic plasmacytoid dendritic cell neoplasm (BPDCN)
C. T-lymphoblastic lymphoma (T-LBL) with aberrant CD33 expression
D. Histiocytic sarcoma

For the solution to the quiz, visit The Hematologist online.
www.hematology.org/TheHematologist/Image-Challenge.

Dr. Gheorghe and Dr. Venkataraman indicated no relevant conflicts of interest.

Figure 1. Low-Power H&E. Extensive, monotonous infiltrate composed of small- to medium-sized cells extending into the dermis. The epidermis is not involved (magnification x400).
Figure 2. High-power H&E. High-power demonstrates blastoid medium-sized lymphoid cells with dispersed chromatin (magnification x100).
Figure 3. CD4 Immunostain (magnification x400).
Figure 4. CD123 Immunostain (magnification x400).

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anticoagulants ranks as the second leading cause of all prescribing errors.4 Furthermore, the landscape of anticoagulation has changed as direct oral anticoagulants (DOACs) have been adopted rapidly and widely as initial therapy for patients with venous thromboembolism and atrial fibrillation, largely replacing traditional agents including warfarin.14,15,16 as a result, there has also been a rise in DOAC-associated AEs and prescribing errors. The Pennsylvania Patient Safety Reporting System investigated DOAC use between January 2011 and August 2017 and identified 1,811 reported AEs, 265 of which resulted in patient harm.17 The most frequent error type without harm was duplicate anticoagulation therapy (33.3%), and others included dose omission, wrong dose, and procedure cancellation. As expected, the most frequent harmful event was bleeding (70.2%), with close to 40% of harmful events occurring in patients who were 80 years or older. Other studies have reported an increasing frequency of DOAC prescribing errors, including incorrect medication dose, lack of dose adjustment for pharmacokinetic problems, and prescription in a patient with a contraindication.18,19

**Joint Commission National Safety Goals to Reduce Harm Associated with Anticoagulant Therapy**

The Joint Commission publishes annual National Patient Safety Goals (NPSGs) designed to identify patient safety priorities and to propose solutions to prevent potential hazards; in 2019, they added six new “Elements of Performance” (EPs) to define goals for health care institutions to improve the safety of anticoagulation therapy (Table). The new document is referred to as NPSG.03.05.01.11 as of July 1, 2019. EPs 1 through 3 include the use of approved protocols and evidence-based practice guidelines for medication selection, reversal and management of bleeding, and perioperative care. EP 4 requires a written policy about laboratory testing to monitor and adjust anticoagulation. EP 5 addresses institutional safety practices, including the development of processes for identifying and responding to adverse drug events. EP6 focuses on patient education, ensuring that patients are aware of medication dose and schedule, follow-up plan, and potential drug interactions and adverse reactions.

**Provided Resources**

Along with the main publication of requirements,10 the Joint Commission also published a compendium of resources,11 including seminal guidelines and publications, to help institutions achieve these patient-safety goals. The list includes online clinical support tools from the Anticoagulation Forum’s Centers of Excellence Resource Center, among others.11 Entering the search term for a given EP (e.g., “EPT”) into the search field of their website11 provides a collection of resources designed to help organizations meet the selected EP. Available materials include clinical protocols, order sets, patient education materials, and “examples of excellence” that highlight successful efforts in organizations across the United States. Also included are newer efforts to build accessible, user-friendly online resources to assist providers such as the ManageAnticoag App (tools.acc.org/ManageAnticoag) created by the American College of Cardiology.12 This application guides users through algorithms for periprocedural anticoagulation interruption and restart (EP 3), addresses acute anticoagulation-induced bleeding (EP 2), and provides a real-time clinical decision tool to support safe anticoagulation prescribing practices. The Joint Commission has also published a “Sentinel Event Alert” with an abbreviated list of recommendations to assist institutions in developing DOAC safe prescribing practices.13

**The Systems-based Hematologist**

With the creation of these new care standards, health systems must now institute efforts to ensure compliance with safe anticoagulation prescribing practices and provide hematologists with the opportunity to lead these efforts. In 2015, ASH partnered with a consulting firm, Levin Group, to investigate the future of nonmalignant hematology, seeking opportunities for nonmalignant hematologists to more effectively contribute in the emerging 21st century health ecosystem.31 In doing so, they identified a new career role — the “systems-based hematologist,” which refers to “a specialty-trained physician, employed by a hospital, medical center, or health system, who optimizes individual patient care, as well as the overall system of health care delivery for patients with blood disorders.”32

The implementation of the new Joint Commission safety goals presents a prime opportunity for further implementation in systems-based hematology across the United States. Multiple institutions have reported improved safe prescribing practices and cost savings with the implementation of multidisciplinary anticoagulation stewardship teams,12,13 and the Anticoagulation Forum recently published very user-friendly new resources to support the development of system-level initiatives to improve anticoagulation safety.14 The full report from the Levin Group highlights the professional role of “Medical Director for Hemostasis/Thrombosis Stewardship,” who would be equipped to create and lead such programs.13 As anticoagulation management has become increasingly complex, having a trained hematologist at the helm can ensure the creation of safe and effective care plans and policies that improve anticoagulation care delivery.

**Take-home Points**

In conclusion, there are three key lessons we should keep in mind. First, the Joint Commission has published six new goals to encourage improvement in the safety of anticoagulation therapy.13,14 Second, a comprehensive document by the Joint Commission lists and links to a wealth of resources, to assist individual hematologists and institutions implement safe anticoagulation prescribing practices.15 Third, the Anticoagulation Forum produced a nice, user-friendly document to assist with implementation of good anticoagulation practices.16 Finally, systems-based hematology is an emerging field in which hematologists work within health care systems to meet these and other patient safety goals to improve hematologic care delivery.

1. The Joint Commission. NPSG.03.05.01 Support Resources. Effective July 1, 2019. Access via https://www.jointcommission.org/NPSG.03.05.01_support_resources/

Dr. May and Dr. Moll have no relevant conflicts of interest.
Despite ongoing efforts for novel therapeutic agents for multiple myeloma (MM), the standard-of-care regimens have heavily relied on proteasome inhibitors (PIs) and immunomodulatory agents (IMiDs) for more than a decade. While there are numerous investigational agents in the clinic, the heterogeneity across all MM subtypes has heavily stalled the success of novel therapeutic agents.

MM is the second most common hematologic cancer and is classified by the bone marrow infiltration of malignant monoclonal immunoglobulin (Ig) -secreting plasma cells. While clinical features, including CRAB (calcium elevated, renal failure, anemia, and bone lesions/pain) symptoms, M-spike, and plasma cell infiltration levels (BMPC), are commonly used to stratify patients’ disease stage, the underlying molecular mechanisms of pathogenesis are often overlooked for targeted therapies. There are current efforts to genetically stratify therapies: for instance the BCL2 inhibitor venetoclax is undergoing phase III clinical trials for a specific subset of patients with MM who harbor the t(11;14) translocation. However, the use of PIs in MM treatment has been effective across all myeloma subtypes, mainly due to leveraging the biology of Ig-secreting plasma cells. Upon elevated demand for Ig secretion, insufficient endoplasmic reticulum (ER) capacity results in the accumulation of unfolded proteins (UPs). Inhibition of the 26S proteasome by PIs creates a backlog of substrates that cannot be effectively degraded, activating the UP response (UPR) and ultimately leading to apoptosis. Thus, the UPR may serve as a potential therapeutic vulnerability across all subsets of patients with MM. One of three ER stress sensors, inositol-requiring enzyme 1α (IRE1α), helps detect UP and alleviates ER stress from the newly increased demand of expected Ig. IRE1α contains a cytosolic kinase domain and tandem endoribonuclease (RNase) domain, which upon activation, cleaves mRNA coding unspliced X-box protein 1 (XBPIu), Upon mRNA cleavage, the newly translated XBPI stimulates numerous genes needed to alleviate the UPR, including protein chaperones and disulfide isomerases.1−5

In a recent article, Dr. Jonathan Harnoss and colleagues genetically and pharmacologically targeted IRE1α and the UPR in MM. The authors showed that a panel of genetically diverse cell lines harbor IRE1α and genetic disruption of IRE1α, or downstream XBPIu, attenuates tumor growth in MM xenograft mouse models. Pharmacologic targeting of the IRE1α kinase domain was achieved through selective small-molecule inhibitors as previously reported. Interestingly, these selective inhibitors also attenuated XBPIu RNAse activity (and further spliced XBPIu mRNA) via a conformational change of the kinase domain (specifically the αC-helix) as determined by X-ray crystallography. This conformational change ultimately afforded allosteric inhibition of IRE1α’s RNAse activity. Previous targeting of IRE1α’s RNase shows that ATP-competitive inhibitors, which do not stabilize a conformational change of the αC-helix (type I and type II inhibitors), can maintain or in some cases activate IRE1α’s RNase activity.6,7 Using these highly selective inhibitors of both IRE1α’s kinase and ribonuclease domain, the authors further show that pharmacologic targeting of IRE1α can attenuate subcutaneous and orthometastatic growth of human MM xenografts in severe combined immunodeficient mice. Furthermore, these compounds can selectively target CD138+ ex vivo MM cells with superior selectivity to nonmalignant CD138− cells. Thus, providing evidence that targeting the UPR via IRE1α may be a successful strategy across all subsets of MM patients.

Since a cure for MM does not exist, novel therapeutic strategies are essential for prolonged survival and favorable clinical outcomes. As we unravel the genomic complexities and molecular mechanisms that govern pathogenesis, novel targeted therapies can follow. PIs, however, are among the most successful agents for MM treatment to date, due in part to their genomically indiscriminate efficacy. They take advantage of a vulnerability of the UPR in highly Ig-secreting plasma cells. This strategy has provided prolonged survival across this heterogeneous disease and suggests a unique mechanism to develop therapies that can be advantageous across multiple MM subtypes. The findings provided by Dr. Harnoss and colleagues offer evidence that targeting the UPR via IRE1α may be a successful therapeutic strategy and further show its compatibility and synergy with standard-of-care PIs. Of note, these inhibitors also have the unique ability to target distal allosteric sites of IRE1α, showcasing the ability to perturb both catalytic and distal protein domains of kinases simultaneously with a single agent. As kinases have been a successful therapeutic target across all cancers, this phenomenon of targeting noncatalytic functions is still in its infancy and can provide kinase inhibitors with enhanced efficacy.8 Therefore, as IRE1α inhibitors make their way to the clinic, both selectivity and impact on allostery should be thoroughly investigated. Therapeutic strategies that can target all myeloma subtypes are still few and far between. However, a highly heterogeneous disease may require a heterogenous drug-toolbox, and selective IRE1α inhibitors are the newest addition.


Dr. Agius, Dr. Tahri, and Dr. Ghobrial indicated no relevant conflicts of interest.
A new patient with diffuse large B-cell lymphoma (DLBCL) has an International Prognostic Index (IPI) of 0 and is told that she has a 90 percent chance of staying in remission two years after completing R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy. A young patient with unmutated IgVH chronic lymphocytic leukemia (CLL) with normal cytogenetics is told that he has a 50 percent chance of maintaining a remission at five years following treatment with FCR (fludarabine, cyclophosphamide, and rituximab). For both patients however, these are just statistics, and they do not provide any insight into whether the patient in front of you will be in the 10 percent of patients with DLBCL who relapse, or whether the patient's unmutated IgVH CLL will relapse within a year of completing FCR. In the era of alternative, non–chemotherapy-based effective therapies for these diseases, better individual predictors of outcome, rather than relying on the presence or absence of relapse over time, has the potential to spare a patient ineffective therapies and to direct them earlier to more effective therapies. This is the power in the Continuous Individual Risk Index (CIRI) developed and validated by Dr. David M. Kurtz and colleagues and published recently in Cell.

CIRI is a dynamic risk assessment that uses established pretreatment and interim-treatment risk factors for specific cancer subtypes to reassess the probabilities of an individual’s overall outcome. In DLBCL, these risk factors include the IPI, cell of origin of the tumor, interim positron emission tomography imaging assessment, pretreatment circulating tumor DNA burden, early molecular response, and major molecular response. In CLL, these risk factors include clinical and cytogenetic risk indices, peripheral blood minimal residual disease, and choice of therapy. Dynamic risk assessment in this system is modeled after “win-probability” models in which risk predictions are continuously assessed over time, considering additionally collected longitudinal data. It has the capacity to make outcome predictions at specific timepoints using a naive Bayes approach, as well as to make longitudinal survival predictions using proportional hazard modeling and Bayesian analysis. In the validation cohorts for both DLBCL and CLL, CIRI closely calibrated to observed outcomes within ±5 percent. In both models, CIRI outperformed any of the individual risk factors. Furthermore, because choice of therapy was considered a risk factor in the CIRI-CLL modeling, CIRI-CLL could be assessed for its predictive power and provides a biomarker for response to a specific therapy. It could indeed predict for benefit from FCR over alternative immune-chemotherapies following a period of induction therapy and an interim biomarker/response analysis. This model is applicable to other cancer subtypes as well; the authors present their modeling following neoadjuvant chemotherapy for breast cancer as an example.


Improving Cancer Prognostication Using Dynamic and Longitudinal Modeling


Single-cell Genomics Reveals the Cellular Landscape of Bone Marrow Stromal Cells


ONIMA CHOWDHURY, PHD, AND ADAM MEAD, MD, PhD

The bone marrow microenvironment is a crucial component of hematopoietic stem and progenitor cell regulation, in both health and disease. Intercommunication between hematopoietic cells and stromal cells is vital, for example, in the expression of cell surface or secreted factors, such as growth factors. Bone marrow stroma is composed of a multitude of heterogeneous cells, including those forming connective tissue and blood vessels, and those giving rise to a variety of supportive tissues including bone, fat, and cartilage. To date, it has been unclear whether the current cellular markers we use to identify stromal cells define truly distinct populations of cells. Definitive characterization of the cellular components of the hematopoietic niches is vital to understanding their interactions with hematopoietic cells in health and disease. Single-cell genomics is a powerful tool to characterize cellular architecture of cell populations such as the bone marrow niche. Dr. Ninib Baryawno and colleagues at Harvard University applied single-cell RNA sequencing to definitively annotate mouse bone marrow stromal cells based on their functional ontogeny profiles. The authors identified and in-depth characterized multiple groups of stromal cells—mesenchymal stem cells (MSCs), osteoclineage cells (OLCs), pericytes, chondrocytes, bone marrow endothelial cells (BMECs), and fibroblasts. They then clustered 17 distinct subpopulations, resolving many new subgroups and providing clarity on how certain populations are developmentally related.

First, the researchers were able to subclassify MSCs into four major subsets, distinguished by their expression of particular genes and elucidating likely pathways of differentiation between the subsets. The authors then enhanced the classification of what was previously determined as a single population of OLCs into two subpopulations with different origins and differing ability to regulate hematopoietic cells. With regard to cartilage formation, five different clusters expressed genes associated with the cartilage-forming lineage, and the authors used bioinformatic techniques to delineate potential differentiation pathways between the clusters of cells. To date, it has been difficult to definitively mesh mesenchymal stem cells from fibroblasts. In this study, however, the authors were able to recognize five distinct subgroups of fibroblasts of varying likenesses to MSCs, from those expressing hematopoietic and niche factors through to tendonogenic/ligamentous cells. Dr. Baryawno and colleagues also defined three distinct subsets of BMECs; all were related to each other along a continuum but expressed different hematopoietic ligands and secreted factors. They further described three pericyte subpopulations, also varying in their expression of key hematopoietic regulators such as CXL12 and Kit.

Following the mapping of bone marrow stromal cells in steady-state normal bone marrow, the authors went on to investigate the impact of acute myeloid leukemia (AML) on the stromal environment. They compared the effect of transplanting healthy mice with either normal bone marrow cells or AML–driven leukemia bone marrow on the bone marrow stromal compartment. These studies demonstrated that AML distorted the stromal environment significantly, with significant changes in the proportions of subpopulations of stromal cells on expression of hematopoietic or ligand-expressing bone marrow cells, including changes in expression of hematopoietic regulators within defined stromal subpopulations. These stromal cell changes were consistent with a model in which leukemia creates an aberrant hematopoietic niche that simultaneously promotes aberrant leukemia cell differentiation and proliferation while suppressing normal hematopoiesis (e.g., via deregulation of vital hematopoietic stem cell niche growth factors, specifically Cxl12 and Kit).

In summary, the authors provide novel insights into cellular heterogeneity of mouse bone marrow stromal cells, providing a comprehensive resource for researchers studying functional roles within the bone marrow niche. They not only define novel subsets of stromal cells but also determine how these populations are related to one another along different differentiation continua and define expression patterns of key hematopoietic regulators. Importantly, this taxonomy was descriptive and almost entirely based on gene expression with manual annotation of putative functions. As the authors acknowledge, current methods do not allow in vivo functional assessment of each identified cell cluster. The presence of the AML cells clearly distorted the stromal environment, which is consistent with a model whereby leukemic cells influence the stromal cells, subverting their differentiation patterns and reducing the expression of regulatory signaling molecules known to be essential for normal hematopoietic function. The next challenge will be to map the spatial relationships between these identified stromal cell types and their hematopoietic niches or leukemia cell infiltrations using emerging imaging and spatial transcriptomic techniques.
FCR while others strongly preferred ibrutinib. While therapy. In my experience, some patients opt for immunochemotherapy versus indefinite targeted
walk them through the pros and cons of finite
than 65 years. For patients meeting those
be an option for select CLL patients, meaning
Based on these considerations, FCR can continue
be very large with low numbers of events, and it
is quite possible the OS signal will diminish with
One might conclude that this trial signals the
BRIAD KAHL, MD
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cancer diagnosed within 3 months or has been treated within 6 months or metastatic.
also a statistical significant overall survival (OS) advantage for ibritni-nib-ruxamib. Of note, FCR performed similarly to ibritni-nib in the patients with mutated IgVH genes. Toxicities for FCR were typical for that regimen. The ibritni-nib-ruxamib regimen was reasonably well tolerated with low levels of grade 3 to 4 toxicity.
One might conclude that this trial signals the death knell for FCR given the OS advantage for ibritni-nib-ruxamib. Before planning FCR’s memorial service, a few considerations merit further thought. First, the overall number of death events was quite low (4 vs. 10). Hazard ratios can be very large with low numbers of events, and it is quite possible the OS signal will diminish with time. Second, this trial allowed participation of patients as old as 70 years, which is pushing the envelope for safe administration of FCR. It would be nice to see the data analyzed by age. There was a statistically significant overall survival (OS) advantage for ibritni-nib-ruxamib. Of note, FCR performed similarly to ibritni-nib in the patients with mutated IgVH genes. Toxicities for FCR were typical for that regimen. The ibritni-nib-ruxamib regimen was reasonably well tolerated with low levels of grade 3 to 4 toxicity.
A bold U.S. intergroup trial has put FCR to the test and identified a worthy replacement in the form of ibritni-nib-ruxamib. Dr. Tait D. Shanafelt and colleagues conducted a randomized phase III clinical trial comparing FCR against ibritni-
ruxamib in 529 patients with previously untreated CLL. Patients needed to meet International Working Group Criteria for therapy and needed to be 70 years or younger to be eligible. Patients with 17p deletion were not eligible. The FCR regimen was administered at the usual dose and was scheduled for six cycles. Ibritni-nib was administered at a dose of 420 mg daily, given until disease progression, while rituximab was administered for six months. Ibritni-nib-ruxamib was more efficacious. With a median follow-up of 33 months, the three-year progression-free survival was 89 percent for ibritni-nib-ruxamib versus 73 percent for FCR. Somewhat surprisingly, there was also a statistically significant overall survival (OS) advantage for ibritni-nib-ruxamib. Of note, FCR performed similarly to ibritni-nib in the patients with mutated IgVH genes. Toxicities for FCR were typical for that regimen. The ibritni-nib-ruxamib regimen was reasonably well tolerated with low levels of grade 3 to 4 toxicity.
This study confirms that a standardized perioperative management strategy for DOACs is safe, with low event rates for major bleeding and arterial thromboembolism. An additional noteworthy finding is that LMWH was not used for bridging. Switching patients from DOACs to LMWH to “bridge” around an invasive procedure does not make pharmacologic sense because the half-life of LMWH is similar to DOACs (8-14 hours). LMWH bridging for warfarin makes sense owing to the much longer half-life of warfarin (40 hours). However, even this practice is questionable given recent data showing that it causes more harm than benefit for most patients.1
Does the PAUSE study answer all of our questions about perioperative management of DOACs? It does not, and in fact, it raises new questions. For example, rivaroxaban did not meet the prespecified threshold for major bleeding of less than 2 percent. Does this mean this agent should be held longer before and/or after procedures? Are these results applicable to dabigatran [with a smaller than planned sample size] or edoxaban (not included)? Is a DOAC-specific level of 50 ng/mL a safe cut point for high bleeding risk procedures, especially if neuraxis anesthesia is required?
Another important observation from the PAUSE trial is the timing of the arterial thromboembolic events. The reported median was postoperative day 2, which is also when the risk of bleeding is still considered high for many procedures. A lower dose of DOAC given on postoperative day 2 might provoke less bleeding, but it is also less effective at preventing arterial thromboembolism. This suggests that at least some of these thrombotic events are not preventable.

**RIP FCR?**


**Pressing PAUSE on Direct Oral Anticoagulants for Patients With Atrial Fibrillation Who Require Invasive Procedures**


BRAD KAHL, MD

Each year, approximately 20 percent of individuals taking a direct oral anticoagulant (DOAC) for stroke prevention will require an invasive procedure. Unfortunately, there is a wide discrepancy in opinion and scant published evidence to guide clinicians on the appropriate duration of treatment discontinuation. Patients and their physicians need to know when to hold an agent prior to procedures and how soon they should be restarted once treatment has concluded. This evidence gap puts patients at risk for thrombotic events as well as postprocedural bleeding.

Dr. James D. Douketis and colleagues performed a multicenter, prospective cohort study (PAUSE) that evaluated the safety of a standardized perioperative management strategy for patients with atrial fibrillation taking DOACs who required an elective surgery or procedure. Apixaban, dabigatran, or rivaroxaban were held for one to four days preoperatively based on the agent, the risk of procedure-related bleeding (high or low according to prespecified classification), and patient renal function. They were restarted two to three days postoperatively depending on the risk of postprocedural bleeding. Therapeutic-dose low-molecular-weight heparin (LMWH) was not permitted, and DOAC levels were not used to guide management. The primary outcome measure for each DOAC-specific cohort was major bleeding and arterial thromboembolism at 30 days.

A total of 3,007 patients with atrial fibrillation (mean age, 72.5 years; mean CHADS2 score, 2) were enrolled (apixaban in 42%, dabigatran in 22%, and rivaroxaban in 36%). One-third of the procedures were classified as high bleeding risk. The 30-day postoperative rate of major bleeding was as follows: apixaban, 1.35 percent (95% CI, 0%-2.00%); dabigatran, 0.90 percent (95% CI, 0%-1.79%); and rivaroxaban, 1.85 percent (95% CI, 0%-2.68%). The 30-day postoperative rate of arterial thromboembolism was as follows: apixaban, 0.16 percent (95% CI, 0%-0.48%); dabigatran, 0.60 percent (95% CI, 0%-1.33%); and rivaroxaban, 0.37 percent (95% CI, 0%-0.92%). All major bleeding events and nine of 10 arterial events (ischemic strokes) occurred a median of two days (interquartile range, 0-6 days) postoperatively. Preoperative DOAC treatment levels were less than 50 ng/mL for more than 90 percent of the subgroup of 2,541 patients who had tested performed.

**Figure. Perioperative Direct Oral Anticoagulant (DOAC) Management Protocol**

**Table 1. Perioperative Direct Oral Anticoagulant (DOAC) Management Protocol**

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Surgical Procedure/Associated Bleeding Risk</th>
<th>Preoperative DOAC Interruption Schedule</th>
<th>Postoperative DOAC Resumption Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>High</td>
<td>Day -5</td>
<td>Day +1</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>High</td>
<td>Day -4</td>
<td>Day +2</td>
</tr>
<tr>
<td>Edoxaban (G黎紹50 mg/day)*</td>
<td>Low</td>
<td>Day -3</td>
<td>Day +3</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Low</td>
<td>Day -2</td>
<td>Day +4</td>
</tr>
</tbody>
</table>

No DOAC was taken on certain days (shaded) and on the day of the elective surgery or procedure. The light blue arrows refer to an exception to the basic management, a subgroup of patients taking dabigatran with a creatinine clearance (C-CI) less than 50 ng/mL. The orange arrows refer to patients having a high-bleed-risk surgical procedure. Dark blue arrows refer to patients having a low-bleed-risk surgical procedure. The thickened orange part of the arrows refer to flexibility in the timing of DOAC resumption after a procedure.

*Cancer diagnosed within 3 months or has been treated within 6 months or metastatic.

This study confirms that a standardized perioperative management strategy for DOACs is safe, with low event rates for major bleeding and arterial thromboembolism. An additional noteworthy finding is that LMWH was not used for bridging. Switching patients from DOACs to LMWH to “bridge” around an invasive procedure does not make pharmacologic sense because the half-life of LMWH is similar to DOACs (8-14 hours). LMWH bridging for warfarin makes sense owing to the much longer half-life of warfarin (40 hours). However, even this practice is questionable given recent data showing that it causes more harm than benefit for most patients.1

Does the PAUSE study answer all of our questions about perioperative management of DOACs? It does not, and in fact, it raises new questions. For example, rivaroxaban did not meet the prespecified threshold for major bleeding of less than 2 percent. Does this mean this agent should be held longer before and/or after procedures? Are these results applicable to dabigatran [with a smaller than planned sample size] or edoxaban (not included)? Is a DOAC-specific level of 50 ng/mL a safe cut point for high bleeding risk procedures, especially if neuraxis anesthesia is required?

Another important observation from the PAUSE trial is the timing of the arterial thromboembolic events. The reported median was postoperative day 2, which is also when the risk of bleeding is still considered high for many procedures. A lower dose of DOAC given on postoperative day 2 might provoke less bleeding, but it is also less likely to be effective at preventing arterial thromboembolism. This suggests that at least some of these thrombotic events are not preventable.

The PAUSE study offers clear evidence-based guidance on how to manage DOACs around invasive procedures. It also provides a warning that clinicians and patients must agree to these procedures with their eyes wide open about the risks.


Dr. Linkins was a data adjudicator for this trial, but was not involved in study design, data analysis, or writing of the manuscript.
Does Your MDS Treatment Have Mettle? The Utility of Iron Chelation Is Always a Point of Discussion in MDS


DeZern indicated no relevant conflicts of interest.

Voxelotor: Changing the Disease by Changing the Conformation


SAMUEL WILSON, MD, IFY OSUNKWO, MD, MPH, KATHLEEN MONANAH, DO, AND JANE LITTLE, MD

Sickle cell disease (SCD) is a global problem, estimated to affect more than 100,000 individuals in the United States and millions of people worldwide.1 SCD results from a single nucleotide substitution in the β-globin chain of adult hemoglobin (HbA), which produces instead the sickle cell hemoglobin (HbS). When the HbS molecules clump together, they form dimers and tetramers of HbS polymers, leading to damage and distortion of the red blood cell (RBC), hemolysis, inflammation, thrombosis, acute vaso-occlusive crisis (VOC), and chronic vascular clogging.2,3 Despite the grim prognosis, iron chelation therapy, in the form of deferoxamine, has been the mainstay of therapy for all patients, especially for those with severe disease.4 RBC transfusion provides prompt, symptomatic relief for lower hemoglobin and improves health-related quality of life. Unfortunately, transfusion dependence is also associated with its own morbidities. The long-awaited TELESTO trial, a randomized controlled trial of deferasirox compared to placebo was published as an abstract (#304) at the 2018 ASH Annual Meeting; it showed a risk reduction in the treatment arm, but no overall survival (OS) benefit with chelation.1 The long-awaited TELESTO trial, a randomized controlled trial of deferasirox compared to placebo was published as an abstract (#304) at the 2018 ASH Annual Meeting; it showed a risk reduction in the treatment arm, but no overall survival (OS) benefit with chelation.1 The noted benefit in deferasirox is interesting, but unfortunately, there was no further information provided on the choice of iron chelation regimen in MDS, making this a significant morbidities. 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A Novel Immunotherapy for T-ALL

CAROLINE DORIO, MD, AND DAVID T. TEACHEY, MD

T-cell acute lymphoblastic leukemia (T-ALL) accounts for approximately 15 percent of pediatric, and 25 percent of adult ALL cases.1 The overall survival rate for pediatric patients currently exceeds 85 percent, but this requires intensive, prolonged therapy with short-term and long-term morbidity. Furthermore, patients with relapsed or refractory disease have a dismal prognosis.2 A powerful novel strategy for the treatment of patients with relapsed or refractory disease is immunotherapy. Immunotherapeutics have been applied to other types of ALL, specifically B-cell ALL (B-ALL), with great success; however, it has been challenging to apply this approach to T-ALL because of issues with fratricide and the inherent toxicities related to targeting T cells. In their recent article, Dr. Julie A. Hixon and colleagues describe a promising potential novel approach for the treatment of T-ALL via targeting the interleukin-7 (IL-7) receptor α (IL-7Rα). They developed a monovalent antibody targeted against IL-7Rα and tested its safety and efficacy in preclinical models.

The investigators developed two murine monoclonal antibodies targeting IL-7Rα (constructs 2B8 and 4A10) and demonstrated their capacity to bind to mutant and wild-type IL-7Rα. Both antibodies were subsequently humanized. In an ex vivo experiment, both constructs effectively killed TALL blasts via antibody-dependent cell-mediated cytotoxicity (ADCC) using natural killer (NK) cells, with a higher effectiveness demonstrated when both constructs were combined. Fractricide of NK cells was not observed.

After demonstrating the effectiveness of both constructs in ex vivo experiments, the investigators used a series of patient-derived xenograft (PDX) models to further evaluate the efficacy and safety of this approach. They first demonstrated the efficacy of both constructs in an artificial leukemia driven by an IL-7Rα mutation that was introduced into immune-deficient mice. They then used a patient sample leukemia (T-ALL#5) to demonstrate the efficacy of the monoclonal antibodies in controlling low levels and high levels of leukemia. They showed that the combination of 4A10 and 2B8 was effective in more samples than either antibody alone. Nevertheless, there was no difference in survival between single and combined antibody administration.

Finally, the authors established the efficacy of the anti-IL-7Rα in PDX models of relapsed T-ALL. PDX mice were treated with daily dexamethasone and vincristine for four weeks, either alone or in combination. Following the completion of treatment, persistent or recurrent blasts were assessed for IL-7Rα expression using flow cytometry and were shown to have increased expression with both single agents and combination therapy. The increase in IL-7Rα was higher in patient samples treated with combination therapy as compared with those receiving dexamethasone alone. Results for mice receiving vincristine alone were not reported. Mice with relapsed leukemia following dexamethasone and vincristine were treated with either a combination of 4A10 and 2B8, or vehicle. Mice treated with the anti-IL-7Rα monoclonal antibody combination had reduced leukemia cells (measured by flow cytometry) 14 days post-treatment (Figure). Treatment with the anti-IL-7Rα monoclonal antibodies improved survival but was not curative. Despite exploring ex vivo testing in four unique samples of TALL, the PDX models used only a single sample (TALL#5). TALL samples are notoriously heterogeneous, and the efficacy demonstrated in TALL#5 has not yet been reproduced. The authors acknowledged this limitation, and further evaluation of T-ALL PDXs is underway. They also evaluated the efficacy of their antibody combination in vivo using T-ALL, using blasts from mice who had been treated with dexamethasone and vincristine in vivo to mimic, albeit imperfectly, relapsed T-ALL in patients. Perhaps the most important concern related to translating this discovery into the clinical realm is the broad expression of IL-7Rα on normal T cells, as T-cell aplasia could be a major toxicity associated with this therapy.

In summary, Dr. Hixon and colleagues developed two monoclonal antibodies targeting IL-7Rα and demonstrated their efficacy when used separately or in combination in ex vivo and in vivo models of T-ALL. Although potential toxicities need to be carefully considered, this study nevertheless represents an important potential breakthrough in the management of relapsed or refractory T-ALL.


Dr. Diorio and Dr. Teachey indicated no relevant conflicts of interest.

Outfoxing OXPHOS

The authors further showed that cytokine depletion disrupts other GSH-dependent processes. Specifically, they examined the effect of cytokine depletion on the glutathionylation of succinate dehydrogenase A (SDHA), a subunit of the electron transport chain complex II (ETC II). The current report shows that cytokine depletion leads to decreased SDHA glutathionylation and ETC II activity, resulting in reduced OXPHOS and death of ROS-low LSCs. Building on these findings, the investigators examined cytokine levels in ROS-low LSCs. From patients with de novo AML who responded to azacitidine and venetoclax and from patients with relapsed/refractory AML who were resistant to azacitidine and venetoclax. They found that cytokine and GSH was depleted in patients who responded to the combination therapy, but not in those who were resistant to the combination therapy. Levels of these therapies may be a potential biomarker of venetoclax response and therapies designed to degrade cytokine may be useful in refractory AML.

Collectively, the results support the likelihood that cytokine metabolism is an essential metabolic process for the LSCs in AML. They remain to be determined if depletion of individual amino acids would be enough to select or eradicate LSCs. Focusing on the fundamental physiologic characteristics of the LSCs and the enzymes that are conserved from patient to patient despite the chromosomal or genetic heterogeneity, may provide a rational treatment approach for those patients with no other “targetable” mutation. Additionally, this study provides further insight into the mechanism of venetoclax resistance.

While a phase III trial testing azacitidine versus azacitidine and venetoclax in relapsed/refractory AML has been conducted (NCT02993523), final results are awaited. It will be of interest to see if the combination results in durable complete remissions as might be expected if LSCs are indeed suppressed by venetoclax plus a hypomethylating agent. Furthermore, this combination has not been tested yet in younger patients, nor has venetoclax been tested in combination with other cytotoxic chemotherapies or in maintenance settings where ongoing LSC suppression would be critical. Focusing on the unique metabolic requirements of LSCs may provide insight into how best to eradicate this OXPHOS-dependent cell as the source of relapse.


Dr. O'Dwyer and Dr. Liesveld indicated no relevant conflicts of interest.
“Cool”

This was Stan’s quintessential email response when you reached out to him about an interesting patient, a recent publication, or a special event in your life. To be honest, just a single word like that would leave you hanging and wanting more — is that really all you got? Those who trained under Stan could expect this online brevity because he was an unfinishing presence at our conferences and dictations. We always had an opportunity to follow up with meaty conversations about life and hematology across the conference table.

As a founding father of Stanford’s Division of Hematology, Stan was the doting parent of a program he helped nurture for six decades and over which he presided as chief for 27 years. He knew that showing up was at least 50 percent of showing that you care. He effectively used sardonic wit and unfiltered wisecracks to theatrically punctuate substantive teaching points.

Stan’s education and mentorship of two generations of hematologists were recognized by the Stanford University School of Medicine’s Albinon Hewlett Award, Stanford University’s Walter J. Gorees Award, and ASH’s Mentor Award.

Stan recounted that the pediatrician who attended to him for colds in his South Bronx home couldn’t do much, but he was caring, and Stan wanted to be like him. Like Stanford colleague Dr. Irwin Weismann and many future physician-scientists, teenager Stan fell in love with the colorful stories of discovery from Leeuwenhoek to Ehrlich, depicted in Paul de Kruif’s Microbe Hunters. His matriculation in the prestigious Bronx High School of Science introduced him to the scientific method and indulged his sense of wonder. After his college years at the University School of Medicine’s 1950 freshman class and interned with the colorful stories of discovery from Leeuwenhoek to Ehrlich, depicted in Paul de Kruif’s Microbe Hunters. His matriculation in the prestigious Bronx High School of Science introduced him to the scientific method and indulged his sense of wonder. After his college years at the University of Pennsylvania and medical school at Stanford, Stan headed west with his wife Peg and was hired as assistant professor in the Division of Hematology at the Stanford University School of Medicine’s newly minted campus in Palo Alto.

Stan started with basic research of the red blood cell (RBC) membrane, studying its structure, function, deformability, and transfer function. However, Stan wanted a clinical outlet; in 1982, he undertook a sabbatical at Hebrew University in Jerusalem to understand the biologic basis of anemia in thalassemia. He led studies that identified the types of excess globin chain accumulation in the membranes of RBCs that led to their premature death, seminal contributions to the understanding of the different pathophysiology of α- and β-thalassemia.

Stan was heavily involved with ASH. During his tenure as ASH President in 2004, he maintained his long-standing interest in mentoring and education. He made a large impact on the Society’s global footprint, including establishing the International Consortium on Acute Leukemia (formerly I-C-APL) in Mexico and several South American countries. His international ambassadorship extended to the Health Volunteer Overseas (HVO) program, where he helped to innovate hematology care programs in Uganda, Peru, and at the Angkor Hospital for Children in Siem Reap, Cambodia.

Stan was also a winemaker who with his son David, spent 40 years honing Chardonnay, Zinfandel, and other varietals in French oak barrels in his cellar, named Cabrillo Springs. While Stan’s product never touched the hands of a sommelier or graced the pages of Wine Spectator, he developed a vintner’s wisdom that doubled as one of his life’s aphorisms: “…the thing you learn when you make wine is patience; nothing happens fast… the mistakes that I’ve made are when I try to hurry things… do not drink the red wine too soon.”

Stan’s tornardic pace in academic hematology did not abate after his “retirement” in 1999. He became the first Hematology Editor for BloodPedia, cofounded the Stanford Amyloidosis Center with Dr. Michaela Liedtke, and remained an active principal investigator on a National Institutes of Health grant on anemia in the elderly. Stan maintained his outpatient clinic, research program, and resident dictations at the microscope until a few months before his passing. He never suffered from a withering of youthful enthusiasm; he rode his bike into his 80s, and at age 90, his boyish sense of wonder never lost any of its sheen.

Stan’s affection for hematology was matched only by the love of the outdoors he shared with his family. His annual camping and backpacking trips to Yosemite were a prep for his and Peg’s trek to Everest base camp in 1982. Stan lost Peg to amyotrophic lateral sclerosis in 2001 and found love again with Barbara Klein. This time, Stan and Barbara introduced the grandkids Andres and Emilia to the national parks, HVO sites and their indigenous peoples, and sanctuaries such as the Galapagos Islands.

While we dearly miss Stan, I’d like to think that if you look hard enough at a meadow of wildflowers, or a glissade down the misty slopes of Mount Rainier, “…the thing you learn when you make wine is patience; nothing happens fast… the mistakes that I’ve made are when I try to hurry things… do not drink the red wine too soon.”

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—Jason Gotlib, MD, MS, Professor of Medicine, Stanford University School of Medicine, Stanford, CA
Primed for Self-Destruction: Adding Venetoclax to Azacitidine for MDS

STUDY TITLE: A Phase 1b Dose Escalation Study Evaluating the Safety and Pharmacokinetics of Venetoclax in Combination with Azacitidine in Subjects with Treatment-Naïve Higher-Risk Myelodysplastic Syndromes (MDS)

CTN NUMBER: NCT02942290

SPONSOR: AbbVie, Inc.

ACCRUAL GOAL: Approximately 80 participants

PARTICIPATING CENTERS: Approximately 30 sites globally

STUDY DESIGN: This trial will enroll adults 18 years and older who have previously untreated de novo MDS with International Prognostic Scoring System (IPSS) risk categories intermediate-2 or high (i.e., minimum IPSS score of 1.5), less than 20 percent bone marrow blasts, Eastern Cooperative Oncology Group performance status of at most 2, currently ineligible for intensive chemotherapy or allogeneic hematopoietic stem cell transplantation (allo-HCT), and white blood cell count of at most 10,000/mL. Patients with therapy-related MDS or MDS/myelodysplasia/secondary neoplasm overlap will be excluded. Treatment will include standard azacitidine 75 mg/m² for seven days either consecutively on days one to seven or with a two-day break (2-2) every 28 days, with venetoclax per dose level (100 mg, 200 mg, or 400 mg) on days 1 to 14, every 28 days. The study is designed to evaluate the safety and preliminary efficacy of the combination of venetoclax and azacitidine. Guided by a Bayesian optimal interval design, dose-escalation will occur at three dose levels. A dose-escalation phase and is accruing to the safety and pharmacokinetics of venetoclax in combination with azacitidine. Secondary objectives are to assess preliminary efficacy data including the overall response rate, duration of response, overall survival, and progression-free survival.

RATIONALE: Management of patients with higher-risk MDS remains challenging owing to the limited approved therapeutic options, median age of onset, and complex disease biology (Papapetrou et al. Blood. 2013;122:3616-3627; Haferlach T, et al. Leukemia. 2014;28:241-247). This clonal disorder is characterized by a set of recurrently mutated genes involved in RNA splicing, epigenetic and traditional transcriptional regulation, and signal transduction (Bejar R, et al. N Engl J Med. 2013;369:2406-2416). While cure can only be achieved by allo-HCT, disease-modifying therapies are necessary for effective cytoreduction and to minimize leukemic transformation. frontline therapy for higher-risk MDS has been limited to hypomethylating agents and in some cases cytokind induction chemotherapy. Clinical trial strategies throughout the past decade have focused on using epigenetic targets and optimizing frontline chemotherapy regimens with novel agents. Despite advances in our genetic understanding of MDS, there has been little change to upfront management of high-risk MDS. Small-molecule inhibitors of mutant isocitrate dehydrogenase enzymes, however, have some clinical activity for a minority of patients (DiNardo CD et al. N Engl J Med. 2018;378:2386-2398). Small-molecule spliceosome inhibitors (Seller M et al. Nat Med. 2018;24:497-504; Steensma D et al. EHA Library. 2019;2666175:PS1304) and pharmacologic reactivation of mutant p53 (Salman BA et al. Blood. 2018;132:3091) are still being investigated.

Incorporating novel agents into treatment with hypomethylating agents (HMA) may be a more promising approach to improve outcomes for higher-risk MDS. Venetoclax is a selective, potent, orally bioavailable, small molecule inhibitor of b-cell lymphoma-2 (BCL-2) that promotes apoptosis by acting as a BCL-2 mimic (Pan R et al. Cancer Discov. 2014;4:362-375). The BCL-2 domain is found in all prosapotic BCL-2 family of proteins. Venetoclax acts by displacing pro-apoptotic proteins such as BIM or BAX from BCL-2 to induce BAX- or BAK-dependent mitochondrial outer membrane permeabilization (MOMP), which commits the cell to apoptosis (Figure; Cigler M et al. Cancer Cell. 2011;20:749-761). This clonal approach to improve outcomes for untreated MDS beyond the current standard of care.

Although data are limited, two studies in AML support the use of venetoclax in MDS. In a phase II venetoclax monotherapy trial for relapsed/refractory AML, the complete remission (CR) plus CR with incomplete blood count recovery (CRi) rate was 19 percent (6 of 32 patients). Notably, half of these responders (3 of 6 patients) had an antecedent hematologic disorder. A second phase Ib study examined venetoclax in combination with the HMA azacitidine for the treatment of newly diagnosed AML in patients ineligible for intensive chemotherapy. The combination therapy resulted in a striking CRi rate of 73 percent in the venetoclax 400 mg plus HMA cohort, leading to the recent accelerated approval of the combination by the U.S. Food and Drug Administration (DiNardo CD et al. Blood. 2019;133:171-177). Although the number of patients with prior/underlying MDS was not explicitly reported, nearly a quarter of the subjects (36 of 145 patients) enrolled on the latter AML trial had a prior hematologic disorder and response rates did not differ among those with de novo and secondary AML. These practice-changing results raise the question of whether this combination has activity in related diseases such as MDS.

Though no dose-limiting toxicities including laboratory or clinical tumor lysis syndrome were reported in the AML setting (DiNardo CD et al. Blood. 2019;133:171-177), it comes as no surprise that gastrointestinal adverse events (AEs) were common and expected given the underlying disease and known AEs associated with HMA use (Fenaux P et al. Lancet Oncol. 2009;10:223-232). One concern about adding venetoclax to azacitidine in the MDS setting is the potential for prolonged neutropenia and associated infectious complications, which was reported in the phase Ib study of frontline venetoclax in combination with azacitidine for AML (DiNardo CD et al. Blood. 2019;133:171-177). To minimize the risk of febrile neutropenia complications, the current MDS study protocol was amended to reduce the duration of venetoclax exposure (continuous 14 days vs. 28 days) to allow for hematologic recovery. Furthermore, dose modifications were implemented to reduce the dose of venetoclax and azacitidine in the event of recurrent prolonged neutropenia. For these reasons, patients will be eligible for infection-related complications and a second dose expansion was built to re-evaluate dosing and scheduling as needed once the optimal venetoclax dose is identified.

By using a combination approach in the upfront treatment of MDS that has been proven effective in secondary AML, this trial represents an effort to continue to reduce the number of patients who ultimately experience disease progression. It is anticipated that patients who were previously ineligible for allo-HCT might become eligible with disease modification and thus come off study treatment.

COMMENT: Results from this MDS trial are highly anticipated given the promising activity and known tolerability of the combination of venetoclax and azacitidine for the elderly population with AML. Though determination of whether and preliminary clinical efficacy of combining venetoclax with azacitidine is the critical question being addressed by this trial, testing the feasibility of BH3 mimetics across myeloid malignancies is of great interest given their large therapeutic window and lack of genotoxicity, which makes them great candidates for combination therapies. The issue of whether a more active combination therapy leads to survival benefit or delays leukemic transformation remains to be seen. This study is accruing well and on target to complete enrollment by the end of 2019.

Planned exploratory correlative studies to identify a biomarker of response include evaluation for the presence or absence of myeloid mutations and BCL-2 family molecular expression (protein or RNA). Recently, this study has cleared the initial dose-escalation phase and is accruing to the safety expansion cohorts. This trial represents a promising approach to improving outcomes for untreated MDS beyond the current standard of care.

— Jacqueline S. Garcia, MD, Anthony Letai, MD, PhD, and Annette S. Kim, MD, PhD

Dr. Garcia received research funding from AbbVie, Pfizer, and Genentech, Dr. Letai received research support and consultation payment from Astra-Zeneca, Novartis, and AbbVie. He has served as a consultant for AbbVie, Genentech, and F. Hoffmann-La Roche and has received grants from AbbVie, Genentech, Eli Lilly, Celgene, Calithera, Stemline, Threshold, Flexus Biosciences, and Novartis. Dr. Kim indicated no relevant conflicts of interest.
Interferon in Low-risk Polycythemia Vera: Does Better Tolerability Allow for Earlier Intervention?

STUDY TITLE: Benefit/Risk Profile of AOP2014 in Low-risk Patients With PV (Low-PV)

CLINICALTRIALS.GOV IDENTIFIER: NCT03003325

PARTICIPATING CENTERS: Italian multicenter study under the leadership of Professor Tiziano Barbi, Fondazione per la Ricerca Ospedale Maggiore di Bergamo (FIRM)

ACCRUAL GOAL: 150 as of February 2, 2017

STUDY DESIGN: Low-PV is a multicenter, randomized phase II trial in a low-risk population of patients with polycythemia vera (PV; e.g., patients < 60 years of age and without previous thromboembolic complications). Patients receive either pegylated proline interferon (IFN) alfa-2b once every two weeks at a single dose of 100 µg versus the comparator of standard therapy (phlebotomy and low-dose acetylsalicylic acid [ASA] 100 mg daily). The primary goal is to compare the number of patients that maintain the recommended hematocrit level of less than 45 percent over 12 months in each arm. Several secondary endpoints include phlebotomy use, hematologic and molecular responses, splenomegaly, thromboembolic and hemorrhagic events, and quality of life (QoL). Eligibility of patients is defined by diagnosis of PV according to the 2016 World Health Organization criteria, age 18 to 60 years, and hematocrit less than 45 percent at study entry. Exclusion criteria include history of previous thromboembolic or cardiovascular events, prior exposure to cytoreductive drugs including IFNs, infections, significant comorbidities, and pregnancies. The study is sponsored by FROM and AOP Orphan Pharmaceuticals.

RATIONALE: Phlebotomy remains a key intervention in patients with low-risk PV; however, its therapeutic limitations and the use of alternative therapies are debated. As there is no consensus definition of phlebotomy resistance, continuing frequent phlebotomies to avoid pharmacologic cytoreduction may result in symmetric iron deficiency. Fine tuning the frequency of phlebotomies to achieve iron deficient erythropoiesis but avoid severe iron deficiency is challenging. IFN therapy is a recommended approach for younger patients with high-risk PV. Early studies described efficacy of IFN at doses of 3 million IU, three times per week. Similar efficacy results can be obtained with pegylated IFN (PEG-IFN). Both PEG-IFN alfa-2a and PEG-IFN alfa-2b have been recommended as an alternative treatment option by international guidelines in Europe and the United States. Pegylation of IFN prolongs serum half-time, thus enabling weekly drug administration. PEG-IFN results in complete hematologic responses in up to 95 percent of patients, together with reduction of JAK2-V617F allelic burden and induction of hematologic remissions. Furthermore, all patients became phlebotomy-free, and this was durable. Unfortunately, about 90 percent of patients experienced IFN-associated adverse effects, including neuropsychiatric, musculoskeletal, and gastrointestinal events, with a high discontinuation rate owing to adverse effects; even higher incidences of IFN therapy discontinuation were reported in other studies. A randomized phase III trial is currently being conducted in the United States to compare PEG-IFN alfa-2a plus low-dose ASA (80-100 mg daily) versus hydroxyurea (HU) plus low-dose ASA in patients with high-risk PV. In this trial, PEG-IFN alfa-2a is applied initially at 45 µg per week and will be gradually increased to 180 µg per week, whereas HU is administered in a dose of 500 mg twice daily (NCT01239856).

Recently, a novel IFN alfa-2b, ropegiferon interferon alfa-2b, with an ultralong elimination half-life has been developed for the treatment of high-risk PV. Promising results could be obtained in a phase II open-label trial of 51 patients. Both the efficacy (overall response rate, 90%; complete molecular response, 21%) and safety of the compound in this study supported the development of the drug in a randomized phase III trial (PROUD-III). The PROUD-III study (N=254) tested twice-weekly subcutaneous injection of ropegiferon alfa-2b compared with daily HU or best available therapy. The three-year results of this randomized trial of untreated or HU pretreated patients with high-risk PV showed superiority of the IFN compound versus the comparator with regard to the rate of complete hematologic remissions and reduction of allelic burden. These results resulted in ropegiferon interferon alfa-2b becoming the only approved drug for high-risk PV in the EU.

To assess the efficacy and tolerability of ropegiferon interferon alfa 2b in low-risk PV, this definitive study is needed to inform physicians about its efficacy and toxicity profile compared to the standard treatment of phlebotomies in combination with low-dose ASA.

COMMENT: The Low-PV trial started enrollment in February 2017 with an expected number of 150 participants. Enrollment is expected to finish by the end of 2019. This trial is significant because it will provide the first evidence of whether treatment with pegylated IFN in low-risk PV might be comparable or superior to repeated phlebotomies to maintain the recommended hematocrit level (< 45%), as well as for tolerability and symptom control. Additionally, by targeting patients with low-risk disease theoretically offers the best opportunity for pegylated IFN to have disease modifying activity. We believe that this trial may inform the future clinical management of patients with low-risk PV.

8. — Florian Heideli, MD, and Steven Lane, MBBS, PhD, FRACP, FRCPath.

Dr. Heidel and Dr. Lane indicated no relevant conflicts of interest.
Would You Identify this Underrecognized Cause of Hemolytic Anemia?

Pyruvate kinase (PK) deficiency may be underrecognized,1 but should be considered in patients with hemolysis who lack evidence of an acquired immune disorder.1,2

Patients with PK deficiency may experience:
- Chronic hemolytic anemia
- Iron overload even without transfusions
- Gallstones, splenomegaly, jaundice

New Testing Program*

Diagnostic testing is now available from ARUP Laboratories — at no cost to the patient.

Find out more online at www.knowpkdeficiency.com/testing

Learn more about ongoing clinical trials at www.ActivateClinicalTrials.com

Patient identification and diagnosis are taking on new importance.

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