Reducing the Likelihood of Harm Associated With Use of Anticoagulant Therapy

JORI MAY, MD, AND STEPHAN MOLL, MD

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

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

| EP 1 | Appropriate drug selection and dosing |
|------|--------------------------------------|
| EP 2 | Management of bleeding                |
| EP 3 | Perioperative management              |
| EP 4 | Laboratory testing                    |
| EP 5 | Adverse event reporting, continuing quality improvement |
| EP 6 | Education of patients                 |

(Cont. on page 7)

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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 voluntary 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 the “gavel” and towards a rigorous longitudinal training pathway for hematologists.

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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, MSC
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 cleaner 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 whitespace 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 knowledge 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. If you feel like it, sit down and write a letter. We would love to hear what you think. Thanks for reading.

What’s New at the 61st ASH Annual Meeting and Exposition?

The 61st ASH Annual Meeting, the premier event in hematology, is taking place December 7-10, 2019, in Orlando. To make the most of your experience at the meeting, take advantage of the many new and improved resources and amenities that will be available:

**Meeting Registration at Airport**
This year, ASH will again provide the convenience of meeting registration upon arrival at Orlando International Airport, as well as retrieval of meeting materials, before attendees proceed to their hotels or the convention center.

**ASH-a-Palooza**
Taking place Friday, December 6, before the annual meeting commencement, ASH-a-Palooza will offer a relaxed, open learning environment for trainees in a festival-like setting with multiple opportunities for microlearning. The 2019 ASH-a-Palooza will take place at Top Golf.

**Wellness at ASH**
To address the topic of resilience and physician burnout over the years, ASH is offering a set of short wellness “microburst” workshops at the annual meeting, nap pods, yoga on Saturday and Monday mornings, and a graphic artist at the 2019 ASH Whiteboard that will illustrate attendees’ thoughts regarding what ASH and their institutions can do to help with wellness issues.

**Free Childcare**
ASH will offer free childcare to help support parents attending the annual meeting, beginning on Friday, December 6, through Tuesday, December 10. Snacks, light meals, and beverages will be provided each day, as well as “Future hematologist” t-shirts. Space is limited, so please register your child by October 30.

ASH Park @ The Plaza
Attendees can catch a breath of fresh air at ASH Park—a meeting and networking space located outside, directly across from the entrance to the Orange County Convention Center (West Building, Hall C Lobby). Attendees can also use this space for relaxing and eating lunch or enjoying some live music.

ASH Alexa
New this year, Alexa will be able to connect you with “live” customer service. Attendees can ask Alexa for room information, session times, details about other ASH annual meeting events, and more.

**Mobile App GPS**
In addition to proving comprehensive session information in the palm of your hand, the annual meeting mobile app will now feature GPS technology to guide you from location to location.

For more on the annual meeting, including housing and registration information and a complete preliminary program, visit www.hematology.org/annual-meeting.
Ask the Hematologist

Immune Thrombocytopenia Purpura Versus Inherited Thrombocytopenia in Adults

ANNE T. NEFF, MD
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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 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 requires a high index of suspicion. There are no current guidelines on when to consider IT, but there are some excellent recent reviews (Table). Many of the disorders do not have a hemorrhagic presentation. If asymptomatic, the low platelet count may be an incidental finding with blood work done for other reasons. Some are syndromic, and comorbidities can provide clues. Most will not respond to immune modulating therapies effective for ITP and are autosomal dominant, but if asymptomatic, other family members are often unaware of their own thrombocytopenia.

Table

| Gene      | Platelet Size | Inheritance | Associated Characteristics                  |
|-----------|---------------|-------------|---------------------------------------------|
| Platelet-production genes |               |             |                                             |
| CBFA2, RUNX1, AML1 | Normal | AD          | Myelodysplasia, AML development |
| GATA-1    | Large         | X-linked    | Dyserythropoietic anemia; thalassemia-like |
| GFI1B     | Large         | AD          | α granule deficiency                       |
| ANKRD26   | Normal        | AD/AR       | “Gray platelet” syndrome; absent α granules, myelofibrosis evolution |
| NBEAL2    | Large         | AD/AR       | “Gray platelet” syndrome; absent α granules, myelofibrosis evolution |
| MYP1H     | Large         | AD          | Nephritis, cataracts, sensorineural hearing loss, elevated LFTs, “Döhle-like” neutrophil inclusions |
| FLNA      | Large         | X-linked    |                                             |
| ACTN1     | Large         | AD          | Low reticulated platelet counts            |
| TUBB1     | Large         | AD          |                                             |
| CYCS      | Normal to small | AD      |                                             |
| GP9       | Large         | AD          | Mono-allelic Bernard-Soulier               |
| WAS       | Small         | X-linked    | Wiscott-Aldrich; severe immune deficiency or thrombocytopenia only |

Gene mutations outside of platelet production

| WWP       | Normal to large | AD          | von Willebrand disease type 2B |
| ABCG5, ABCG8 | Large         | AR          | Sitosterolemia, stomatocytosis, xanthomas |
| ADAMTS13  | Normal         | AR          | Congenital TTP, hemolytic anemia, schistocytes, low ADAMTS13 activity |

Abbreviations: AD, autosomal dominant; ADAMTS13, a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; AML, acute myeloid leukemia; AR, autosomal recessive; LFTs, liver function tests; TTP, thrombotic thrombocytopenic purpura. Developed from Novis P and Piccio A.*

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 IT 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.

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. 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.

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Revisiting the History of Haploidentical Transplantation

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The year 1968 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.1 He was an early user of nitrogen mustard for hematologic malignancies2 and one of the first to incorporate its use in autologous transplantation.3

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. The son-in-law was friends with Phyllis Hurtwitz, a hematology fellow at Mount Sinai who had convinced the patient to visit Dr. Dameshek. The son-in-law recalled 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 that 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.4 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.5

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 ×400).

Figure 2. High-power H&E. High-power demonstrates blastoid medium-sized lymphoid cells with dispersed chromatin (magnification ×100).

Figure 3. CD4 Immunostain (magnification ×400).

Figure 4. CD123 Immunostain (magnification ×400).

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

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

A Skin Lesion in a Pediatric Patient: A Close Call

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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 sparing 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, CD33, 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.
anticoagulants ranks as the second leading cause of all prescribing errors.6

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;10,11 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.3

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 percent 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.8,9

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 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 abbreviated list of recommendations to assist institutions in developing DOAC safe prescribing practices.12

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.13

In 2015, ASH partnered with a consulting firm, Lewin Group, to investigate the future of nonvillainous hematologist, seeking opportunities for nonvillainous hematologists to “not only contribute in the emerging 21st century health ecosystem.”14 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.”15

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,16,17 and the Anticoagulation Forum recently published very user-friendly resources to support the development of system-level initiatives to improve anticoagulation safety.18 The full report from the Lewin Group highlights the professional role of “Medical Director for Hemostasis/Thrombosis Stewardship,” who would be equipped to create and lead such programs.18

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.18 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.19 Third, the Anticoagulation Forum produced a nice, user-friendly document to assist with implementation of good anticoagulation practices.20 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.

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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-spikes, 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.1 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.1,2 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.3 Thus, the UPR may serve as a potential therapeutic vulnerability across all subsets of patients with MM. One of the ER stress sensors, inositol-requiring enzyme 1α (IRE1α), helps detect UP and alleviates ER stress from the newly increased demand of rescued Igs. IRE1α forms a cytosolic kinase domain and tandem endoribonuclease (RNase) domain, which upon activation, cleaves mRNA coding unspliced X-box protein 1 (XBP1u). Upon mRNA cleavage, the newly translated XBP1 stimulates numerous genes needed to alleviate the UPR, including protein chaperones and disulfide isomerases.4,5

In a recent article, Dr. Jonathan Hannoss and colleagues genetically and pharmacologically targeted IRE1α and the UPR in MM. The authors showed that a panel of genetically diverse cell lines all harbor IRE1α and genetic disruption of IRE1α, or downstream XBP1, attenuates tumor growth in MM xenograph 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 XBP1u ribonuclease activity (and further spliced XBP1u mRNA) via a conformational change of the kinase domain (specifically the C-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 activity showed that ATP-competitive inhibitors, which do not stabilize a conformational change of the C-helix (type I and type II inhibitors), can maintain or in some cases activate IRE1α’s ribonuclease activity.4,6 Using these highly selective inhibitors of both IRE1α’s kinase and ribonuclease domains, 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 therapeutic strategy across all subsets of MM patients.

Since no 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 genotypically 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. Hannoss 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.4 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, and may rely upon modulating the UPR axis. Ultimately, it is still unclear whether the next standard-of-care treatments will be tailored targeted therapies, pan-MM agents, or some combination of the two. However, a highly heterogeneous disease may require a heterogeneous drug-toolbox, and selective IRE1α inhibitors are the newest addition.

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A new patient with diffuse large B-cell lymphoma (DLBCL) has an International Prognostic Index (IPI) of zero 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 outcome over time. 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 na"ive 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 power as a predictive biomarker for response to a specific therapy; it indeed could 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.

One of CIRI’s weaknesses is that inherent in this model is the initiation of established standard-of-care therapies for the disease in question. Our DLBCL or CLL patient ideally would want to know before even starting a therapy whether it will benefit them in a meaningful way. However, in two important ways it is a significant improvement over just waiting for a relapse. First, it may help to identify a group of patients at the end of standard-of-care therapy, to identify patients for whom this therapy is unlikely to produce lasting benefit, we can over just waiting for a relapse. First, it may help to identify a group of patients at the end of standard-of-care therapy, to identify patients for whom this therapy is unlikely to produce lasting benefit, we can

From Wan JCM, White JR, Diaz LA Jr. “Hey CIRI, What’s My Prognosis?” Cell. 2019;178:518-520. Used with permission.

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

Baryawno N, Przybylski D, Kowalczyk MS, et al. A cellular taxonomy of the bone marrow stroma in homeostasis and leukemia. Cell. 2019;177:1915-1932.

Tbe bone marrow microenvironment is a crucial component of hematopoietic stem and progenitor cell regulation, in both health and disease. Intercellular communication between hematopoiesis 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 niche 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 transcription profiles. The authors defined and putatively grouped clonal populations of stromal cells — mesenchymal stem cells (MSCs), osteolineage cells (OLCs), pericytes, and chondrocytes — bone marrow endothelial cells (BMECs), and fibroblasts. They identified 17 distinct subpopulations, reshaping 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 defined as a single population of bone marrow stromal cells 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 study mesenchymal stem cells from fibroblasts. In this study, however, the authors were able to recognize five different subsets of fibroblasts of varying likeliness to MSCs, from those expressing hematopoietic niche factors to those expressing mesenchymal or mesenchymal-like factors.

Dr. Baryawno and colleagues also defined three distinct subsets of BMECs; all were related to each other along a continuum but express different hematopoietic ligands and secreted factors. They further described three pericyte subpopulations, also varying in their expression of key hematopoietic regulators such as CXCL12 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) macroenvironment. They compared the effect of transplanting healthy mice with either normal bone marrow cells or MLL-AF9–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 bone marrow cells, including those 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 Cxcl12 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 bone marrow stromal niche. They not only define novel subsets of stromal cells but also determine how these populations are related to one another along differentiation continuums 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 defined 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. This next challenge will be to map the spatial relationships between these identified stromal cell populations and hematopoietic or leukemia cell subpopulations using emerging imaging and spatial transcriptomic techniques.

The Hematologist: ASH News and Reports

Dr. Choudhury and Dr. Mead indicated no relevant conflicts of interest.
RIP FCR?
Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. N Engl J Med. 2019;381:432-443.
BRAD KAHL, MD

For many years, standard of care first-line treatment of chronic lymphocytic leukemia (CLL) has been the FCR (fludarabine, cyclophosphamide, rituximab) regimen, which was pioneered for CLL at MD Anderson Cancer Center in large phase II trials and generated impressive results. The efficacy of the regimen was validated by the German CLL study group in phase III trials. Three separate research groups demonstrated the long-term efficacy of the regimen, publishing data sets showing a majority of patients remaining in first complete remission beyond five years. Yet, many practitioners who have used the regimen have discovered its drawbacks. It is both myelosuppressive and immunosuppressive, significantly so. I have quite a bit of experience with the regimen and have witnessed patients become transfusion dependent for as long as a year after FCR, and who never recovered normal blood counts. The risk for opportunistic infections is substantial and can manifest several years after treatment. Finally, there is a small but real risk (approximately 9%) of developing myelodysplastic syndromes/acute myeloid leukemia. Given the drawbacks of this highly efficacious therapy, the CLL community has been anxious to develop new frontline strategies.

A bold U.S. intergroup trial has put FCR to the test and identified a worthy replacement in the form of ibrutinib-rituximab. Dr. Tariq D. Shanafelt and colleagues conducted a randomized phase III clinical trial comparing FCR against ibrutinib-rituximab 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. Ibrutinib was administered at a dose of 420 mg daily, given until disease progression, while rituximab was administered for six months. Ibrutinib-rituximab was more efficacious. With a median follow-up of 33 months, the three-year progression-free survival was 89 percent for ibrutinib-rituximab versus 73 percent for FCR. Somewhat surprisingly, there was also a statistically significant overall survival (OS) advantage for ibrutinib-rituximab. Of note, FCR performed similarly to ibrutinib-rituximab in the patients with mutated IgVH genes. Toxicities for FCR were typical for that regimen. The ibrutinib-rituximab regimen was 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 ibrutinib-rituximab. Before planning FCR’s memorial service, a few considerations merit further thought. First, the overall number of death 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. Third, patients in IgVH-mutated CLL performed similarly to ibrutinib-rituximab for efficacy. Finally, ibrutinib is an expensive, chronic therapy, while FCR is finite.

Based on these considerations, FCR can continue to be an option for select CLL patients, meaning those with mutated IgVH genes and younger than 65 years. For patients meeting those criteria, it is a complicated discussion. One must walk them through the pros and cons of finite immunochemotherapy versus indefinite targeted therapy. In my experience, some patients opt for FCR while others strongly prefer ibrutinib. While the discussions are long and complex, at least we have options, which is always a good problem.

LORI-ANN LINKINS, 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%-2.85%). 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%-0.82%). 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

| DOAC | Surgical Procedures-Arterial Bleeding Risk | Postoperative DOAC Resumption Schedule |
|------|---------------------------------------|---------------------------------------|
| Apixaban | High | Day-1 | Day +1 |
| Dabigatran | Low | Day-5 | Day-4 |
| Rivaroxaban | Low | Day-6 | Day-5 |

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 thrombotic surgical procedure. Dark blue arrows refer to patients having a low-bled-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 important and 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 more 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.

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 neuroaxis 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.

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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

Hoeck M, Yu G, Langemeijer S, et al. Impact of treatment with iron chelation therapy in patients with lower-risk myelodysplastic syndromes participating in the European MDS registry. Haematologica. 2019; doi:10.3324/haematol.2018.212332. (Epub ahead of print)

AMY E. DUZERI, MD, MHS

Despite numerous advances in the care of patients with myelodysplastic syndrome (MDS) in recent years, chronic red blood cell (RBC) transfusions remain the quintessential therapy of choice for these patients, especially those with advanced disease.1 RBC transfusion provides prompt, symptomatic relief for lower hemoglobin and improves health-related quality of life. Unfortunately, transfusion dependence is also associated with less favorable outcomes.2 Chronic transfusion therapy is associated with the risk of iron overload, which has the potential to cause substantial organ toxicity. No controlled prospective studies have demonstrated a benefit from iron chelation in MDS, but several retrospective or observational studies have suggested improved survival with chelation.3 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. Thus, there remains no consensus on the optimal in-hospital chelation regimen in MDS, making this a regular manuscript topic in the literature as we try to optimize outcomes in our patients.

In this study, Dr. Marijn Hoeck and colleagues used the robust European Union MDS (EUMDS) registry to investigate the role of iron chelation therapy in patients with lower-risk MDS. For this analysis, prospectively collected, observational data from recently diagnosed lower-risk MDS patients were included. Of the 199 patients analyzed, patients, chelated or nonchelated, who were eligible for chelation based on at least one of the following criteria: at least 15 cumulative RBC units, transfusion intensity of a one or more units of RBCs per month for a six-month period, median baseline ferritin level of greater than 1,000 µg/L. The registry was queried July 2017 for patients diagnosed between December 2007 and April 2017. This cohort ultimately included 689 eligible patients – 199 chelated and 490 nonchelated. There were many significant differences between chelated and nonchelated patients including older age and increased deaths for nonchelated patients but with longer follow-up for chelated patients. Nonchelated patients had more cumulative RBC units transfused than chelated patients (4 vs. 2 units) at baseline, but the chelated patients had higher median ferritin levels. The median time on chelation was 12 months for 105 patients. Subsequently, recording of reasons for cessation of chelators was not possible in this cohort.

A Cox proportional hazards model showed a hazard ratio (HR) for OS in chelated patients (adjusted for multiple appropriate covariates) of 0.50 (95% CI, 0.34-0.74). Additionally, a propensity score–match modeled a further significantly improved OS for chelated patients, with an HR of 0.42 (95% CI, 0.27-0.63) compared to nonchelated patients. Of the 197 chelated patients, 150 received deferasirox as the initial chelating agent (of the 3 available in Europe at the time). Interestingly, patients who were initially chelated but had second-line chemotherapy or deferoxamine were also counted as deferasirox-treated patients. Compelling analyses were run to investigate improvements in hemopoiesis and even transfusion independence. More than 80 percent of the 77 chelated patients who were responsive to deferasirox also on nonchelated patients. This indicates that the real-world, transfusion-dependent group of patients in their seventh and eighth decades with all the anticipated comorbidities that could be excluded from a trial population. Given its conduct in Europe and not the United States, these lower-risk patients were not routinely treated with hypomethylating agents, and thus their effect on response or myelosuppression did not contribute to the results. Additionally, the propensity score–matched analysis can incorporate more confounding factors into their model. The authors also make the salient point that there will always be limitations to performing a randomized controlled trial for the use of chelators in MDS due to staunchly held beliefs by both providers and patients on the topic. The noted benefit in deferasirox is likely disease modifying, analogous to an increase in hemoglobin (Hb) in patients on hydroxyurea or with an associated increase in transfusion independence in patients with advanced MDS. For this analysis, prospectively collected, observational data from recently diagnosed lower-risk patients. Of the 199 patients, 150 received deferasirox (61%), and improved anemia in a phase II/III clinical trial, chelation was overall well tolerated at a dose of 1,000 mg daily, with reduction in anemia and hemoglobin.3

The HOPE trial was an international effort, with a primary endpoint defined as the percentage of patients with an increase in total Hb of 1 g/dL at 24 weeks, although treatment extended up to 72 weeks. Secondary endpoints included mean change in Hb, incident rate of VOC, and transfusion independence. The results were included in a trial of 197 patients. Individuals eligible for the study were between the ages of 12 to 65 years. All MDS subtypes were eligible, but more than 85 percent of patients studied had HbS or HbSS3. Crucially, individuals on hydroxyurea were not excluded. The authors enrolled 274 patients in an 1:1:1 fashion to treatment groups receiving either voxelotor 1,500 mg, voxelotor 900 mg, or placebo.

Key findings in this trial were significant improvement in anemia and a possible improvement in hemopoiesis, without undue near-term toxicity. In the intention-to-treat analysis, there was a significantly higher proportion of patients with a mean Hb response in the voxelotor 1,500 mg group (51%; 95% CI, 41-61) than in the placebo group (7%; 95% CI, 1-12; p <0.001). The 900 mg dose had an intermediate effect. Secondary endpoints showed a possible decrease in hemoglobin (% induction of peripheral reticulocytes, decreased sickling, and treatment with no significant reduction in lactate dehydrogenase and absolute reticulocyte count). There was no difference between groups regarding percentage receiving RBC transfusion, and there was a nonsignificant reduction in annualized VOC in voxelotor-treated patients versus the placebo group. Safety data were encouraging as most adverse events reported were grade 1 or 2, with diarrhea and headache being the most common. Adverse events of grade 3 or higher did not differ between groups.

Despite the significant opportunism engendered by the HOPE trial, caveats remain that should be fully explored before voxelotor is universally adopted. Safety risks not fully evaluated in the HOPE trial include potential beneficial effects on the renal cortex, which is highly dependent on oxygen delivery, and vascular diseases. As Drs. Robert Hebbel and Bo Hedlund point out, physiology is not linear, and an increase in Hb may not translate to an increase in tissue oxygen delivery, especially with agents that affect oxygen affinity. Sickling in oxygen-dependent cells also on HbS, which has been associated with increased risk for VOC and osteonecrosis and is expected to be a mainstay in conjunction with hydroxyurea (HU). Previous viscosity measurements for voxelotor, normalized to a Hct of 30 percent, showed improvement in viscosity,11 but this may not reflect in vivo changes at true Hct values. Finally, the effect of voxelotor on additional clinically meaningful endpoints such as quality of life and frequency of VOC will need to be established.

The HOPE trial showed that voxelotor had great potential for mitigating hemoglobin levels of individuals with SCD and its downstream effects. However, as with any new agent, it is only with careful study and vigilant observation in the first years of its use that we will truly understand the best and safe ways to use voxelotor.

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A Novel Immunotherapy for T-ALL

Hixon IA, Andrews C, Kashi L, et al. New anti-IL-7Rα monoclonal antibodies show efficacy against T cell acute lymphoblastic leukemia in pre-clinical models. Leukemia. 2019;doi: 10.1038/s41375-019-0531-8. [Epub ahead of print.]

CAROLINE D'ORIO, MD, AND DAVID T. TEACHY, 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. Immune therapies 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-7Ra). They developed a monoclonal antibody targeted against IL-7Ra and tested its safety and efficacy in preclinical models.

The investigators developed two murine monoclonal antibodies targeting IL-7Ra (constructs 2B8 and 4A10) and demonstrated their capacity to bind to mutant and wild-type IL-7Ra. Both antibodies were subsequently humanized. In an ex vivo experiment, both constructs effectively killed T-ALL blasts via antibody-dependent cell-mediated cytotoxicity (ADCC) using natural killer (NK) cells, with a higher effectiveness demonstrated when both constructs were combined. Fratricide 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-7Ra mutation that was introduced into immune-deficient mice. They then used a patient sample leukemic T-ALL#5 to demonstrate the efficacy of the monoclonal antibodies in controlling low levels and high levels of T-ALL blasts and 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-7Ra 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-7Ra expression using flow cytometry and shown to have increased expression with both single agents and combination therapy. The increase in IL-7Ra 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 valproic (a histone deacetylase inhibitor) in combination with anti-IL-7Ra showed reduced leukemia cells (measured by flow cytometry) 14 days post-treatment (Figure).

Treatment with the anti-IL-7Ra monoclonal antibodies improved survival but was not curative. Despite exploring ex vivo testing in four unique samples of T-ALL, the PDX models used only a single sample (T-ALL#5). T-ALL samples are notoriously heterogeneous, and the efficacy demonstrated in T-ALL#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 the anti-IL-7Ra against 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-7Ra 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-7Ra 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 nonetheless represents an important potential breakthrough in the management of relapsed or refractory T-ALL.

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Dr. D'Orio and Dr. Teachey indicated no relevant conflicts of interest.
Boy, Wonder: Stanley L. Schrier, MD (1929-2019)

“Cool”

This was Stan’s quintessential email response when you reached out to him about an interesting patient, 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 have? Those who trained under Stan could expect this online brevity because he was an unflinching presence at our conferences and didactics. 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 wiscracks 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 Albion Walter Hewlett Award, Stanford University’s Walter J. Gores 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 too 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 and Ehrlich, depicted in Paul de Kruif’s Boy, Wonder. Dr. Beutler at the University of Chicago. These were formative interactions that Stan must have thought could provide the prologue of his own origin story, Red Blood Cell Hunters. In 1959, Stan attended the Stateville Penitentiary in Joliet, Illinois, as a senior assistant surgeon who oversaw University of Chicago–led clinical trials with prisoner volunteers trying to figure out how to understand the biologic basis of anemia inthalassemia.

He led studies that identified the types of excess globin chain accumulation in the membranes of RBCs that led to their premature death, seminal contributors to the understanding of the different pathophysologies 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 monitoring and educating patients. He made a large impact on the Society’s global footprint, including establishing the International Consortium on Acute Leukemia (formerly IC-APL) in Mexico and several South American countries. His international ambassadorship extended to the Health Volunteer Overseers (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 Cabernet Sauvignon. Stan was also a winemaker who with his son David, spent 40 years honing Chardonnay, Zinfandel, and Cabernet Sauvignon. While we dearly miss Stan, I’d like to think that if you look hard enough at the misty fog from Mount Shasta, or Yosemite Valley, you just may be able to see the stealthy cabin that he’s claimed behind some dense pines. Stan soaks in the morning sun, inhales the mist and pines. Stan soaks in the morning sun, inhales the mist and pines. Stan soaks in the morning sun, inhales the mist and pines. Stan soaks in the morning sun, inhales the mist and pines.

I M E M O R I A M

Barbara Klein. This time, Stan and Barbara introduced the grandkids Andrea and Enrico into national parks, HVO sites and their indigenous peoples, and sanctuaries such as the Galápagos Islands.

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“Never touch the hands of a sommelier or grace 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 you do hangs on you hanging and wanting more — is that really all you have?”

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 wiscracks 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 Albion Walter Hewlett Award, Stanford University’s Walter J. Gores Award, and ASH’s Mentor Award.

For patients aged 18 to 54 years, disease-free survival was lower with reduced-intensity regimens. Nonrelapse mortality did not differ according to regimen intensity (hazard ratio [HR], 1.34; 42% vs 51%; p=.007) and relapse was higher (HR, 1.32; 42% vs 31%; p=.11) did not differ according to regimen intensity. Disease-free survival was lower with reduced-intensity regimens (HR, 0.64; 20% vs 31%; p=.02). Myeloblastic regimens are preferred for AML, ALL, and MDS; reduced-intensity regimens should be reserved for those unable to tolerate myeloablative transplantation.

From Solomon SR, et al. Blood Advances. 2019;3:2836-2844. More available at www.bloodadvances.org.
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-Naive 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/myeloproliferative 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 (5-2-2) 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 safety expansion cohort will evaluate safety and efficacy at the preliminary recommended phase II dose (RP2D), and a second expansion cohort, if necessary, will evaluate alternative scheduling.

**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 (Papaemmanuil 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. 2011;364:2496-2506). 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 cytotoxic 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 higher-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;5665:FS1034) and pharmacologic reactivation of mutant p53 (Sallman DA et al. Blood. 2018;132:3091) are still being investigated.

Innovating 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 BHC mimetic (Pan R et al. Cancer Discov. 2014;4:362-375). The BHC 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; Ciceri G et al. Cancer Cell. 2009;6:351-365; Potter DS et al. Cold Spring Harb Symp Quant Biol. 2016;81:131-140; Konopleva M et al. Blood. 2018;132:1007-1012). This readiness to undergo apoptosis indicates how “primed” the tumor cells are for BCL-2 inhibition. Priming can be determined by the functional assay called BHC profiling (Deng J et al. Cancer Cell. 2007;12:171-185), which exposes the cancer cell’s mitochondria to synthetic BHC peptides that mimic the prosapotic function of BHC-only proteins to determine MOMP and apoptosis initiation. Results from BHC profiling of myeloblasts correlated with clinical response to venetoclax in acute myeloid leukemia (AML; Konopleva M et al. Cancer Discov. 2016;6:1106-1117).

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). 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).

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 this preliminary clinical efficacy of combining venetoclax with azacitidine is the critical question being addressed by this trial, testing of BHC metrics 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 correlation 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.

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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:** NCT01003325

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

**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 acetaminolysis 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 level 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 Rom 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 significant 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.1 Similar efficacy results can be obtained with pegylated IFN (PEG-IFN).2 Both PEG-IFN alfa-2a and PEG-IFN alfa-2b have been recommended as an alternative to hydroxyurea by evidence-based society 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 50% of patients, together with reduction of JAK2 V617F allele burden and induction of hematologic remissions.2,3 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 (NCT01259856).

Recently, a novel IFN alfa-2b, ropeginterferon 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 I/II open-label trial of 51 patients.2 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 (NCT-254) tested twice-weekly subcutaneous injection of ropeginterferon 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 allele burden.2 These results resulted in ropeginterferon alfa-2b becoming the only approved drug for high-risk PV in the EU.

To assess the efficacy and tolerability of ropeginterferon 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 it provides 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.

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—Florian Heidel, MD, and Steven Lane, MBBS, PhD, FRACP, FRCPA

Dr. Heidel and Dr. Lane indicated no relevant conflicts of interest.

**SEPTEMBER 26, 2019**

Upreti H, Kasmani J, Dane K, et al. Reduced ADAMTS13 activity during TTP remission is associated with stroke in TTP survivors. Blood. 2019;134:1037-1045.

This study shows that the increased occurrence of stroke in thrombotic thrombocytopenic purpura (TTP) during remission is associated with low ADAMTS13 values.

**OCTOBER 3, 2019**

Müller-Calleja N, Hölsherbach A, Ritter S, et al. Tissue factor pathway inhibitor inhibitor priming increases antiphospholipid antibody-induced thrombosis. Blood. 2019;134:1119-1131.

Antiphospholipid antibody syndrome is caused by antiphospholipid antibodies (aPLs) that cause thrombosis through pregnancy loss. In a Plenary Paper, Dr. Nadine Müller-Calleja and colleagues dissect the complex and multifaceted mechanism by which aPLs induce thrombosis through priming of monocytes and disruption of the balance of tissue factor activation and inhibition.

Chen R, Zinzani PL, Lee HJ, et al. Pembrolizumab in relapsed or refractory Hodgkin lymphoma: 2-year follow-up of KEYNOTE-087. Blood. 2019;134:1144-1153.

Dr. Robert Chen and colleagues report excellent durability of response in two patients responding to pembrolizumab for relapsed Hodgkin lymphoma.
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

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* While Agios provides financial support for this program, all tests and services are performed by the selected third-party. Agios receives contact information for healthcare professionals who submit tests under this program and limited de-identified aggregate data.

¹ Grace RF, et al. Am J Hematol. 2015;90(9):825-30. ² Hirono A, et al. Chapter 182 Pyruvate Kinase Deficiency and Other Enzymopathies of the Erythrocyte. New York, NY: McGraw Hill. 2014.