Is the Future of the Benign Hematology Consult Electronic?


A
s the volume of nonmalignant hematologist consults grows and the potential provider pool of nonmalignant hematologists shrinks, questions on how to expand the care of patients with hematologic disorders have become increasingly pressing.1

In a recent letter to the editor published in Blood, Dr. Ashok Pai and colleagues presented the results of their effort to meet this need with a virtual nonmalignant hematology consultation service, commonly referred to as an electronic consultation (e-consult), across five medical centers within the Kaiser Permanente health system in California. With this program, all nonurgent consults were submitted via an electronic portal, while any urgent or inpatient consults continued to be called directly to a physician. One hematologist triaged consult requests for two to three medical centers a week for a at week, determining whether the request could be answered electronically (with chart review and documentation of recommendations in the medical record) or whether an in-person appointment was needed. The triaging hematologist was equipped with tools including consensus recommendations, ordering panels for the laboratory workup of common disorders, and pre-populated templates for frequently asked questions. A weekly conference was also set up to discuss challenging cases and differences in opinions between providers.

In a seven-month trial period, 2,013 consults were submitted for a wide range of nonmalignant hematologic disorders, with an average range of 18.2 to 32.7 consults per day across the five medical centers. Most consults (79%) were managed electronically. Of the consults that required in-person evaluation, most were for blood count abnormalities that warranted further evaluation, often a bone marrow biopsy. Response to consults was timely, with 90.3 percent addressed within 24 hours, and in-person appointments arranged within seven days of request. The average time for a hematologist to complete an e-consult was 14.5 minutes (95% CI, 14.0-14.9). A survey of participating hematologists revealed a high level of satisfaction in both referring physicians and hematologists.

Other practice environments have similarly incorporated e-consult in recent years. Dr. Michael Coccighn and colleagues at the Veterans Affairs Connecticut Healthcare System were first to publish results on hematology e-consult, reporting that consult volume increased while in-person consultation decreased by 18 percent, with a similar mean time of e-consult completion of 14.5 minutes (SD, 7.3) compared to 30 to 60 minutes allotted for in-person appointments.2

Despite these successes, many questions remain regarding the role of e-consult in the future of nonmalignant hematologist within the United States health care system as a whole. Dr. Pai and colleagues practice in a capitated payment model with a shared electronic medical record (EMR), and therefore have existing means for reimbursement and interprovider communication. E-consult becomes more complex in fee-for-service models, but this system is evolving as well. As of 2019, the Centers for Medicare & Medicaid Services (CMS) has included current procedural terminology (CPT) codes for what is termed “interprofessional internet consultation,” thereby creating an avenue for e-consult billing.3 However, challenges of interinstitutional variation in EMRs remain.

Furthermore, the effects of e-consult on consult volume and patient outcomes require further investigation. Results from Dr. Coccighn and colleagues suggest that e-consult decreased in-person consultation volume but significantly increased total consult volume, raising concerns that the ease of requesting an e-consult may increase the collective workload of the consultant.4 Additionally, the need for physicians to spend even more time in EMRs, reviewing, documenting, and communicating electronically, may have negative consequences; increased clerical burden, which is heavily influenced by the extensive use of EMRs, has already been identified as the top factor contributing to physician burnout.5 Finally, neither study evaluated whether more rapid access to subspecialist input would translate to additional patient benefits.

(Cont. on page 2)

Is Hematology Having an Identity Crisis?

RAKHNI P. NAIR, MD, MHS,1 AND ALFRED I. LEE, MD, PhD 2

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2. Associate Professor of Medicine, Yale University School of Medicine, New Haven, CT

In the United States, hematology seems to have lost its identity. Ask any medical student or resident if they are interested in specializing in hematology, and instead of an answer, the inevitable first response will be, “Do you mean oncology?”. In the era of combined adult hematology-oncology training programs in the United States, the standard term among trainees has become “hem-onc,” or more commonly, just “onc.” This terminology confusion extends well beyond trainees. Funding for academic hematology-oncology centers is often derived from federal or private cancer-directed grants, a reality that has resulted in the gradual disappearance of the term “Blood” from “Blood & Cancer Center.”

While on the surface this shift may seem subtle and inconsequential, it may be having a tremendous impact on the academic hematology workforce. A 2007 study sponsored by the American Society of Clinical Oncology projected a deficit in the U.S. hematology-oncology workforce expected to last at least through the following decade.6 Data from the American Medical Association’s Physicians Masterfile and the American Board of Internal Medicine (ABIM) indicate that in the past 15 years, the number of U.S. physicians identifying as hematologists or seeking certification in hematology has been far outpaced by those identifying as medical oncologists or seeking oncology certification.7 In the field of hematopoietic stem cell transplantation specifically, a workforce deficit has also been projected.8

In nonmalignant hematology, however, the workforce trends are even more dire. In 2003, an ASH-sponsored survey of adult hematology-oncology fellowship program directors revealed that less than 5 percent of graduates maintain a primary clinical focus in nonmalignant hematology — a number that remained markedly low in a 2018 single-institution fellow alumni survey.9 From a research perspective, the number of new 801 grants submitted through the Blood Diseases Division of the National Heart, Lung, and Blood Institute (NHLBI) decreased nearly 60 percent from 2000 to 2013, representing a more drastic drop than that seen in other disciplines.10

Given the widespread concerns about the future of hematology, ASH established a Recruitment and Retention Working Group in 2017 to assess the current and future state of hematology as a specialty.

(Cont. on page 2)
Global Thoughts Become Global Actions

Bread diseases span borders, and it’s important that ASH does, too. We are committed to helping hematologists conquer blood diseases worldwide. This is our tagline — one that is both inspirational and aspirational. This worldwide mission is reflected by our membership, which comes from nearly 150 countries, and 41 percent of the nearly 30,000 2018 Annual Meeting attendees came from outside of the United States, which is truly impressive.

Since 2018, one of the eight elected councillor positions on the ASH Executive Committee is reserved for a non-North American member, which is important in helping the leadership understand the needs of our international members. Many of our international efforts are coordinated through the International Members Committee, chaired by Dr. Theresa Cortez from South Africa, and international members populate nearly every ASH executive committee, task force, and editorial. The council-in-chief and incoming deputy editor of our flagship journal, Blood, are non-North American, as are nearly half of the associate editors.

At a high level, the international footprint of ASH is broad and highly impactful, supporting research, education, training, and patient care, with significant focus on building capacity in less developed regions. A great strength of ASH is our ability to convene diverse groups to tackle difficult problems by facilitating collaboration and the exchange of information. Examples include the International Consortium on Acute Leukemia in Latin America, the Children’s International Consortium on Acute Leukemia in the Caribbean, and the Latin American Aplastic Anemia Registry. As part of our major initiative in sickle cell disease (SCD), ASH is working with a variety of partners, including the United States Department of Health and Human Services, to help reduce the burden of SCD in Sub-Saharan Africa. ASH supports development of an African Newborn SCD Screening and Early Intervention Consortium in Africa, and in July, the Society convened a very productive meeting of the Consortium in Johannesburg. Plans are now advancing to launch newborn screening efforts in the initial three countries by this fall. Overall, we saw many valuable opportunities for networking among clinical and governmental champions representing a growing list of African countries.

Another ASH international success story is the Highlights of ASH (HOA) meetings held in Latin America, Asia Pacific, and, beginning in 2019, the Mediterranean. These meetings are held in partnership with hematology societies around the world, bringing content experts from ASH to these sites to distill and share hematology research with the highest clinical impact from the ASH annual meeting with hematologists who were not able to travel to the U.S. I was fortunate to participate in the meetings in Athens and Lima this year and was very pleased to see the enthusiastic engagement by the attendees. This year, these meetings touched more than 1,800 international members, and our partners in these regions unite to work on endeavors worthy of ASH support. In 2019 for example, hematologists from societies throughout Latin America convened in Lima for a full day prior to the new ASH evidence-based guidelines on venous thromboembolism for Latin American hematologists. Adapting guidelines can be an effective strategy to bring trustworthy, context-appropriate recommendations to settings other than those for which they might have been originally intended, at a lower cost.

ASH efforts to support training of hematologists also have an international scope. The Clinical Research Training Institute (CRTI) and Translational Research Training in Hematology (TRTH) provide important education and mentorship for early-career hematologists worldwide. TRTH is co-sponsored by the European Hematology Association and is held in Europe; HOA in Latin America includes a pre-meeting workshop for trainees modeled on CRTI and we are exploring the possibility of expanding trainee opportunities at HOA in Asia-Pacific. One hundred fifty international trainees were supported by ASH this year to attend HOA. ASH has developed several unique training programs focusing on hematology-related needs in developing countries, including the Visitor Training Program (VTP) and the Latin American Training Program (LATP), which are designed to help build hematology capacity in low- and middle-income countries. The two programs provide funding for hematology-related health care professionals to receive up to 12 weeks of training on a specific topic or technique. We recently granted 18 awards to hematologists from Benin, Cambodia, Egypt, Ethiopia, India, Kenya, Myanmar, Nigeria, Pakistan, Peru, Philippines, and Romania. The LATP similarly granted eight awards to hematologists from Argentina, Brazil, Cuba, Mexico, and Peru.

The ASH International Outreach Initiative provides nearly 200 hospitals and universities in low- and middle-income countries with online access to free educational materials to help address needs in these countries with regard to research, practice, and training. Awards are an important benefit to ASH members, and international members are eligible for many, including several travel awards given to presenters of high-scoring abstracts. In 2018, we introduced the ASH Global Research Award (www.hematology.org/GlobalResearchAwards), designed to support future international scientific leaders, increase hematology capacity, and nurture global collaboration. Like the ASH Scholar Award, the Global Research Award supports hematologists between completion of their training and the establishment of their independent careers. The most recent awardees came from Brazil, China, Croatia, Czech Republic, Ghana, Italy, Japan, and Uganda.

Many of the outstanding programs described in this column are supported in part by the ASH Foundation. I encourage all ASH members to consider the Foundation in annual philanthropy planning and to note that there are opportunities to designate all or parts of donations to the Foundation for specific programs, including the Sickle Cell Disease Initiative Fund and the Global Programs Fund.

The ASH portfolio of international activities is broad and deep, and the contributions by our international members to our mission are substantial. As noted by author and New York Times op-ed commentator Thomas Friedman, the world is indeed flat. I am grateful to the leadership and the membership of ASH for mirroring this reality through their contributions. It is this commitment that ensures that our tagline is more than words on a page.

REFERENCES


2019 Honorific Award Winners

At each year’s ASH annual meeting, the Society bestows its most prestigious awards on those hematologists whose work has had a profound influence on the field. Read on to learn more about the 2019 Honorific awardees, their contributions to hematology, and when and where each award will be presented this year in Orlando.

WHO: Richard Aster, MD, Medical College of Wisconsin and Verast Blood Center of Wisconsin
WHAT: Wallace H. Coulter Award for Lifetime Achievement in Hematology
WHERE: Hall D, Orange County Convention Center
WHY: Dr. Aster is recognized for his significant contributions to the understanding of immune diseases that affect blood cells, especially those involving platelets. He has contributed to the development of clinical standards for the diagnosis of immune thrombocytopenia and hemoglobin-induced thrombocyto- penia-thrombosis, moving the field forward through research, mentorship, and education throughout his 82-year career.

WORDS OF WISDOM: “Many hematologic disorders, genetic or otherwise, were among the first to have their pathogenesis elucidated, and effective treatments developed because blood is so readily accessible and easy to work with in the laboratory. This is still true today, and anyone interested in a medical research career would do well to consider hematology as a stepping stone. Life (and biology) is now much more complicated than it used to be, so for a career in laboratory-based research, a combined MD-PhD degree is almost essential.”

WHO: Sriram Krishnaswamy, PhD, Children’s Hospital of Philadelphia and Perelman School of Medicine, University of Pennsylvania School of Medicine
WHAT: Ernest Beutler Lecture and Prize
WHERE: Monday, December 9, 2019, at 1:30 p.m.

WHERE: Hall D, Orange County Convention Center
WHY: Dr. Krishnaswamy will be recognized for his studies of mechanisms by which proteins interact to regulate enzyme function, predominantly in the context of blood coagulation. He is an internationally acclaimed authority on the function of surface-dependent coagulation complexes, which are the targets of new anticoagulants, and has helped set the stage for establishing new therapeutic opportunities for the development and application of novel anticoagulants including aptamers and novel nonanticoagulant site anticoagulants.

WORDS OF WISDOM: “The future of hematology promises the development of new technologies to solve complex biological questions and innovative strategies to treat complex human diseases. Many of the low hanging fruit may be gone, but the difficult questions remain. The keys to this will be broad thinking and broad support for the next generation of scientific advancement. Solutions to these big questions require enthusiastic, creative, and talented investigation into basic and translational science.”

WHO: Jeffrey I. Weitz, MD, McMaster University
WHAT: Ernest Beutler Lecture and Prize
WHERE: Monday, December 9, 2019, at 1:30 p.m.

WHERE: Hall D, Orange County Convention Center
WHY: Dr. Weitz is being recognized for his work in clinical and translational science, namely research on why blood clots occur in certain situations, such as in patients with cancer or those with mechanical heart valves, and how to prevent or treat them. His work has helped develop and licensing of new anticoagulants that streamline the prevention and treatment of thrombosis.

WORDS OF WISDOM: “This is an exciting time for hematologists and there are so many avenues, including those in anticoagulation, hemophilia management, and the treatment of immune diseases. Thus, the ideal choice for those we want to bridge laboratory investigation with clinical advances. It is also important to note that support, training, and networking opportunities are increasing. Pick up those who early-career professionals build skills and relationships within the field.”

WHO: William Eaton, MD, PhD, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH)
WHAT: Henry M. Stratton Medal
WHERE: Tuesday, December 10, 2019, at 9:30 a.m.

WHERE: Hall D, Orange County Convention Center
WHY: Dr. Eaton is receiving this award in recognition of his pioneering biochemical and biophysical research into sickle cell disease pathophysiology and drug therapy. He described the sickle hemoglobin polymerization reaction that causes red blood cell sickling and delineated the protective effects of fetal hemoglobin. His research contributed to the development of hydroxyurea, which helps slow sickling of red cells by inducing fetal hemoglobin synthesis, and the creation of a sensitive test for measuring the time it takes for a blood cell to sickle.

WORDS OF WISDOM: “Follow your passion. The vast body of knowledge that has been established over the years is really only the tip of the iceberg. As you learn more and grow in your career, you will find that your questions are really just the beginning. Stay curious and ask questions. Many of the greatest and most important discoveries have emerged from curiosity.”

WHO: Richard A. Larson, MD, University of Chicago
WHAT: Henry M. Stratton Medal
WHERE: Tuesday, December 10, 2019, at 9:30 a.m.

WHERE: Hall D, Orange County Convention Center
WHY: Dr. Larson has made significant discoveries in understanding the genetic basis of leukemia and translating it into more effective treatments, inspiring him to develop strategies to translate the laboratory science that he has engaged in for the past 40 years into clinical practice. He is a pioneer in the development of oral anticoagulants that streamline the prevention and treatment of thrombosis.

WORDS OF WISDOM: “There are exciting times, not just for those of us working to improve outcomes for malignant blood diseases but across the spectrum of hematologic disorders. Hematology offers tremendous opportunities for overlap with vascular biology, transplantation, immunology, infectious diseases, and many other important areas such as global health. My advice would be to try to learn as much as possible about the biology of your disease of interest, assemble a collaborative network, and think creatively about how to test treatment strategies and special interventions to improve the outcomes in patients.”

WHO: Emmanuel Passegue, PhD, Columbia University Irving Medical Center
WHAT: William Damashek Prize
WHERE: Tuesday, December 10, 2019, at 9:30 a.m.

WHERE: Hall D, Orange County Convention Center
WHY: Dr. Passegue is being recognized for her pivotal contributions to the understanding of the biology of blood-forming stem cells. She discovered a potential strategy for correcting impaired blood production in older people by identifying specific biological mechanisms that are altered when stem cells age and become dysfunctional. She also defined the unique susceptibility of stem cells to specific types of DNA damage and described how their particular repair mechanisms can render them vulnerable to disease-causing mutations.

WORDS OF WISDOM: “Go for it! [Hematology] is an exciting field that is at the forefront of important fundamental and clinical discoveries and it is a mature enough field with established guidelines to make meaningful discoveries. It is a great training ground with outstanding mentors that respect diversity, and it is also a lot of fun.”

WHO: Philip Greenberg, MD, Fred Hutchinson Cancer Research Center and University of Washington in Seattle
WHAT: E. Donald Thomas Lecture and Prize
WHERE: Monday, December 9, 2019, at 9:00 a.m.

WHERE: Hall D, Orange County Convention Center
WHY: Dr. Greenberg is being awarded this lecture and prize in recognition of his pioneering contributions to the development of T-cell adoptive immune therapy, the process by which T cells are equipped with receptors that target and eradicate disease cells. He established the concept and mechanisms of isolating antigens-specific T cells in the laboratory and reproducing them in the numbers needed to observe their activity for targeting a malignancy in vivo, which has allowed researchers to explore the biology of blood cells in detail to better understand how they function, and the obstacles that may interfere with their activity.

WORDS OF WISDOM: “Opportunities are greater than they have ever been. Whether it be T-cell therapy or pharmacology and medicinal chemistry with small drug molecules, if you are following the data that is available, the knowledge about how to treat hematologic malignancies. I believe it is essential to get adequate basic training to participate in these efforts, to pick a question or problem to solve that appeals to you, and to run with it!”

WHO: Griffin Rodgers, MD, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH)
WHAT: ASH Award for Leadership in Promoting Diversity
WHERE: Sunday, December 8, 2019, at 1:30 p.m.

WHERE: Hall D, Orange County Convention Center
WHY: Dr. Rodgers is recognized for his work to achieve broad representation of diverse populations both in the scientific workforce and among clinical trial participants, as well as to increase diversity in NIDDK.

WORDS OF WISDOM: “Follow your passions. This is true in my own life, and it is true in the lives of my colleagues. Staying true to yourself is the only way to be your best in medicine, science, or any other part of your life. Never lose touch with what first inspired, stimulated, and excited you about medicine and about the field you choose because it will take you places you may not think you can go.”

WHO: Michael R. DeBaun, MD, Vanderbilt University School of Medicine
WHAT: ASH Mentor Award
WHERE: Sunday, December 8, 2019, at 1:30 p.m.

WHERE: Hall D, Orange County Convention Center
WHY: Dr. DeBaun is being recognized for his profound influence on his mentees’ intellectual growth and career development. He has mentored people at all education levels, from high school students with sickle cell disease (SCD) to renowned faculty members at multiple medical schools. His mentees have attained academic leadership positions nationally and internationally, becoming leaders of SCD research teams studying prevention of strokes in children with SCD in Nigeria and researching how to decrease pregnancy-related deaths in women with SCD in Ghana.

WORDS OF WISDOM: “Know yourself and what makes you unique. Treat your daily life like a race and wake up early in the morning to advance the care of your patients. Then, have fun doing the hard work!”

WHO: Leonard Zon, MD, Harvard Medical School and Boston Children’s Hospital
WHAT: ASH Mentor Award
WHERE: Sunday, December 8, 2019, at 1:30 p.m.

WHERE: Hall D, Orange County Convention Center
WHY: Dr. Zon receives this award in recognition of his mentorship of trainees who have gone on to establish their own funded laboratories or clinical programs. He mentors people at all stages of their careers including students and technicians, as well as faculty members, through workshops and techniques. He has coordinated events such as a postdoc mentoring breakfast and “technician’s tea” and has developed core modules focused on topics such as developing a laboratory’s budget, practicing an elevator pitch, writing a grant, and presenting at meetings.

WORDS OF WISDOM: “My daughter is now applying for hematology/oncology fellowships this year. I told her to work with the best mentors she can find and then use her skill set to be the best mentor she can be.”
The Case

A 48-year-old woman presents for evaluation of relapsing acquired thrombotic thrombocytopenic purpura (TTP) that has been present since age 30 years. Her initial diagnosis of TTP occurred with a presentation of microangiopathic hemolytic anemia, thrombocytopenia, and neurologic symptoms. At the time of her initial episode, ADAMTS13 levels were undetectable, and an ADAMTS13 antibody was documented. She received plasma exchange and glucocorticoid therapy. This initial course was prolonged owing to relapse upon cessation of plasma exchange therapy. She was administered one dose of vincristine and achieved remission with complete recovery of platelet count and normalization of ADAMTS13 level. Steroid therapy was weaned.

Three years later, the patient experienced a relapse and rapidly responded to plasma exchange and glucocorticoid therapy. She would ultimately have a total of eight relapses. Rituximab has been variably administered in conjunction with plasma exchange for her relapses. Her most recent relapse occurred one month before this encounter; at that time, her ADAMTS13 levels were undetectable, and the ADAMTS13 antibody was present. She was treated with plasma exchange therapy plus four weekly doses of rituximab. She was not treated with glucocorticoid therapy owing to a previous diagnosis of avascular necrosis of the hip, and limited steroid exposure was preferred.

The Question

What is your approach to acquired TTP with multiple relapses?

Response

Acquired TTP is a rare thrombotic microangiopathy that occurs primarily in adults. The condition is characterized by hemolytic anemia and thrombocytopenia resulting from the inhibition of von Willebrand factor–cleaving protease ADAMTS13 by autoantibodies. ADAMTS13 cleaves the large von Willebrand factor multimers in plasma to a greater ability to bind to platelets, leading to microvascular platelet thrombosis.

The standard-of-care treatment of TTP is plasma exchange to replenish functional ADAMTS13 and to remove abnormal von Willebrand factor multimers and ADAMTS13 autoantibodies. Immunosuppressive therapy, typically glucocorticoids, are administered in association with plasma exchange to suppress ADAMTS13 autoantibodies. The addition of rituximab is typically considered for patients who do not demonstrate a rapid response to plasma exchange. Caplacizumab was recently approved for use in acute TTP management. Caplacizumab is a novel humanized, bivalent, immunoglobulin fragment that targets the A1 domain of von Willebrand factor preventing interaction with the platelet glycoprotein Ibα-V-IX receptor and the ensuing microvascular thrombosis. Used in combination with plasma exchange and glucocorticoid therapy in patients with acute TTP, patients receiving caplacizumab demonstrated more rapid normalization of platelet counts, reduced TTP relapse, mortality, and a lower rate of relapsed TTP during the clinical trial than those on the placebo arm.

After remission is achieved for an acute presentation of TTP, a risk of lifetime recurrences persists. Relapses most often occur within the first year of the initial diagnosis but can occur up to 20 years later. Following an initial episode of TTP, a significant percentage of patients will, over time, demonstrate a recurrence of the ADAMTS13 antibody and falling ADAMTS13 levels. For patients with ADAMTS13 levels that drop below 10 percent, the likelihood of relapse over the course of years approaches 75 percent.

In patients who have had one or more relapses, the goal of therapy is to prevent additional relapses. Following serial ADAMTS13 and ADAMTS13 antibody titers in such a patient is helpful in assessing the risk of a clinical relapse.

A variety of immunosuppressive therapies, including rituximab, cyclophosphamide, cyclosporine, bortezomib, mycophenolate mofetil, and N-acetylcysteine, have been used to prevent recurrences. The best studied of these is rituximab; recent data from a prospective registry showed that “pre-emptive” administration of rituximab when ADAMTS13 levels dropped below 10 percent was associated with a significant decrease in the clinical relapse rate.

Case reports and small case series also detail the utility of splenectomy in the setting of multiple relapses. Long-term remissions have been reported in patients undergoing splenectomy, though adverse events including postoperative TTP relapse have been reported, necessitating very close monitoring of patients throughout the postoperative period.

Patient Follow-Up

After a discussion of options, the patient will be monitored monthly with a complete blood count and ADAMTS13 level testing. If ADAMTS13 levels decline to 10 percent, rituximab will be administered to prevent a clinical relapse. Should rituximab ultimately prove ineffective or have a short-lived benefit, the strategy can be altered with consideration of other immunosuppressive agents. Additionally, elective splenectomy was discussed and will be reserved for the future should immunosuppression prove ineffective at preventing relapses.

Should a clinical relapse occur, plasma exchange will continue as the mainstay of urgent therapy, with the consideration of adding caplacizumab. Given the complication of avascular necrosis, glucocorticoid therapy will continue to be deferred.

A 42-year-old white man presented with jaundice and generalized edema. He had been diagnosed with alcoholic cirrhosis four months prior. Laboratory evaluation is summarized in the Table. Abdominal ultrasound revealed a nodular liver and splenomegaly of 15.6 cm in craniocaudal dimension. Peripheral blood smear (panel A) revealed spur cells (acanthocytes, arrows). Hospital course was complicated by hematemesis and acute kidney injury requiring dialysis.

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<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Reference Range</th>
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</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>8.8 g/dL</td>
<td>14-17 g/dL</td>
</tr>
<tr>
<td>Mean cell volume</td>
<td>100 fL</td>
<td>81-96 fL</td>
</tr>
<tr>
<td>Platelet count</td>
<td>11 x 10^11/L</td>
<td>150-425 x 10^11/L</td>
</tr>
<tr>
<td>White cell count</td>
<td>11.4 x 10^9/L</td>
<td>4.5-11 x 10^9/L</td>
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<td>Reticulocytes</td>
<td>5%</td>
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</tr>
<tr>
<td>Ferritin</td>
<td>955 ng/mL</td>
<td>22-350 ng/mL</td>
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<tr>
<td>Creatinine</td>
<td>0.75 mg/dL</td>
<td>0.4-1.3 mg/dL</td>
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<tr>
<td>Blood urea nitrogen</td>
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<td>14.2/5.6 mg/dL</td>
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<td>International normalized ratio (INR)</td>
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<td>0.9-1.1</td>
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<tr>
<td>Fibrinogen</td>
<td>69 mg/dL</td>
<td>200-400 mg/dL</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>&lt;30 mg/dL</td>
<td>44-215 mg/dL</td>
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Which of the following will reverse this patient’s anemia?
A. Rituximab
B. Steroids
C. Liver transplantation
D. Red cell exchange

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

Drs. Shomali, Fernandez-Pol, and Gotlib indicated no relevant conflicts of interest.

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

CONVERSATION STARTER

**Spur Cell Anemia**

WILLIAM SHOMALI, MD, 1 SEBASTIAN FERNANDEZ-POL, MD, PhD, 2 AND JASON GOTLIB, MD, MS 3

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3. Professor of Medicine, Division of Hematology, Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA

A 42-year-old white man presented with jaundice and generalized edema. He had been diagnosed with alcoholic cirrhosis four months prior. Laboratory evaluation is summarized in the Table. Abdominal ultrasound revealed a nodular liver and splenomegaly of 15.6 cm in craniocaudal dimension. Peripheral blood smear (panel A) revealed spur cells (acanthocytes, arrows). Hospital course was complicated by hematemesis and acute kidney injury requiring dialysis.

**Table. Laboratory Evaluation**

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<tr>
<td>Fibrinogen</td>
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<td>Haptoglobin</td>
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<td>44-215 mg/dL</td>
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For the solution to the quiz, visit The Hematologist online, www.hematology.org/TheHematologist/Image-Challenge.

Drs. Shomali, Fernandez-Pol, and Gotlib indicated no relevant conflicts of interest.

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

**Featured content from Blood Advances, Volume 3, Issue 15**

**A Phase II Study of Brentuximab Vedotin in Patients With CD30-positive Advanced Systemic Mastocytosis**

There is an unmet need for effective therapies for advanced systemic mastocytosis (advSM). CD30 is expressed on the surface of neoplastic mast cells (MC) in more than 50% of patients with advSM. Brentuximab vedotin (BV) is a CD30-directed antibody-drug conjugate with preclinical evidence supporting both an antineoplastic effect and an attenuation of immunoglobulin E-associated mediator release. These observations are the basis for this phase II trial of BV monotherapy (1.8 mg/kg IV every 3 weeks up to 8 cycles) in patients with CD30-positive advSM. The primary objective was to determine the efficacy of BV according to International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis (IWG-MRT-ECNM) response criteria. Secondary objectives included evaluation of safety, changes in bone marrow (BM) MC burden, serum tryptase level, flow cytometric quantification of MC surface expression of CD30, and self-reported symptom burden. The trial enrolled 10 patients with a diagnosis of CD30+ advSM (aggressive SM, SM with an associated hematologic neoplasm, or mast cell leukemia) with 1 or more signs of SM-related organ damage. According to IWG-MRT-ECNM criteria, none of the patients demonstrated better than stable disease with BV...


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The Bone Marrow Microenvironment in Myelodysplastic Syndromes

LAURA M. CALVI, MD, AND JANE L. LIESYELD, MD

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2. Professor of Medicine, Hematology/Oncology Division, James P. Wilmot Cancer Institute, University of Rochester School of Medicine and Dentistry, Rochester, NY

The bone marrow microenvironment is known to play a role in the regulation of normal hematopoietic stem cells (HSCs). In recent years, many laboratories have contributed mechanistic data identifying different cellular constituents and signals that regulate not only the most primitive HSCs, but also more differentiated progenitors. From this work, we know that the bone marrow microenvironment is heterogeneous, with multiple niches likely supporting heterogeneous stem and progenitor pools. Concurrently, targeting the cancer microenvironment has revolutionized the treatment strategy for patients with solid organ tumors. However, with the notable exception of multiple myeloma, in which the role of the microenvironment has long been acknowledged and targeted, in other cancers of the hematopoietic system, current therapeutic strategies focus primarily on the diseased clone. In this Mini Review, we discuss the current understanding of the role of the bone marrow microenvironment in myelodysplastic syndromes (MDS), disorders with often dismal prognosis and few approved and effective treatment modalities, with the aim of advancing for novel therapeutic opportunities targeting the microenvironment.

Conceptual and Experimental Arguments for the Role of the Microenvironment in MDS Pathogenesis

Recent work has highlighted the mutational heterogeneity of MDS. Data show that most mutations are represented in both low- and high-risk MDS, and that multiple mutations are often present in the same individual.1 While efforts should certainly be aimed at targeting the clonal mutations, focusing on the bone marrow microenvironment may provide a strategy based on stereotyped interactions of clonal cells with mesenchymal and immune cell populations2,3 in the marrow that may cooperate with individual mutations in determining disease pathology and outcomes. Such approaches could complement clone-directed therapy. Conceptually, certain characteristics of MDS suggest a role of the microenvironment in contributing to disease pathogenesis. Notably, MDS cells support the concept that the cell of origin for MDS is within the stem cell pool—a population typically thought to be more resistant to mutations. Yet in MDS there is clonal expansion in the setting of mutations that ordinarily would not provide an intrinsic advantage at least in vitro.6 In addition, a large body of work is showing the importance of inflammation in MDS.7 For example, aberrancies found in MDS (5q–) and also in clonal hemopoiesis of indeterminate potential (Tet2 mutations) are capable of initiating an inflammatory program that can be acquired by normal bone marrow mesenchymal cells.8,9 To date, however, strategies to target these inflammatory signals have not been extensively tested in therapeutic settings.

Impact of Microenvironmental Disruption on Signals That Support HSCs

Studies of the bone marrow microenvironment have revealed a dominant role of mesenchymal-osteolineage cells in the production of critical HSC maintenance factors such as CXCL12, KIT ligand (stem cell factor), and angiopoietin-1.10,11 These signals contribute to regulation of HSC retention, proliferation, and differentiation that are necessary for maintenance of hematopoietic homeostasis. With MDS-induced dysfunction of this supportive mesenchymal cell population, decreased HSC function would be expected to follow.12 Indeed, genetically altered murine models have demonstrated that defects in mesenchymal and osteoprogenitor populations are sufficient to drive the expansion of not only MDS but also acute myeloid leukemia and myeloproliferative neoplasms.13-15 In the setting of myeloproliferative neoplasms or MDS, in murine models and human samples, the microenvironment demonstrates decreased HSC-supportive signals, including decreased CXCL12, increased stromal cell senescence, abnormal remodeling of blood vessels, osteoblastic defects, and marrow neural damage. It is also the source of disruptive inflammatory signals such as transforming growth factor-β (TGF-β), the alarmins S100A8 and S100A9, interleukin-1 (IL-1), and the chemokine CCL3.16-18 Data have also shown that some of these inflammatory mediators may be generated by the MDS clone.19,30 Therefore, numerous signals from the microenvironment have already come to light that could cooperate with clonal mutations and could represent potential therapeutic MDS targets.

Microenvironmental Targeting Strategies

Identification of the signals that govern reciprocal interactions of MDS and the bone marrow microenvironment is ongoing, and some of the recently identified targets are already being studied, often by repurposing therapies previously approved for other disorders. For example, identification of activation of the inflammasome (NLRP3) in 5q– MDS provides rationale for examining the impact of TLR/TRAf6 inhibitors, NLRP3 inhibitors and IL-1 signaling inhibitors. Similarly, inhibitors are available for TGF-β and chemokines such as CCL3, making therapeutic targeting of the microenvironment feasible.

It is our opinion that several factors limit the impact of this work in MDS. First, the genetic heterogeneity of MDS and the frequent co-occurrence of mutations make MDS difficult to model in vivo. Whether different mutations or their combinations induce unique microenvironmental responses remains unknown and should continue to be an active area of research. Second, one of the key populations responsible for HSC support (mesenchymal stromal cells) are extremely rare and remain poorly defined in the human marrow, with lack of consensus as to isolation and definition of these populations. Therefore, studies identifying these populations are often difficult to compare. However, given the availability of agents to potentially target MDS-microenvironment reciprocally signals, the potential for novel therapies that could finally change MDS prognosis by rationally targeting both the MDS clone and its microenvironment to drive discovery and clinical investigation.

Acknowledgements: The authors thank their laboratory members and Dr. Michael W. Becker for helpful discussion. Supported by funds from the Department of Defense, the Mangurian Foundation, the Taub Foundation, and funds from the James P. Wilmot Cancer Institute.


The Hematologist. ASH NEWS AND REPORTS


**Figure**


**Table**

<table>
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<th>Drug Name</th>
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<td>AGI-4780</td>
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<tr>
<td>Ivosidenib</td>
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**References**


**Dr. Harding and colleagues raises the possibility of dual IDH inhibition at the outset of therapy to prevent clonal evolution and evasion. Lastly, there are important pathology ramifications of these studies. They highlight the importance of whole coding sequence coverage of genes of targeted therapies, rather than hotspot single gene assays or multiplex panels, as well as the importance of coverage of relevant biologic isoforms as well.**

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**Figure**

Structure of an IDH2 inhibitor (AGI-4780, structurally related to enasidenib andivosidenib) allosterically bound at the homodimerization interface in cellulo with the IDH2 R140Q protein. (Reprinted with permission from Chen J, Yang J, Sun X, et al. Allosteric inhibitor remotely modulates the conformation of the orthosteric pockets in mutant IDH2/R140Q. Sci Rep. 2017 Nov 28;7:16458. http://creativecommons.org/licenses/by/4.0/)
Diagnostic Algorithm Reduces the Need for Radiation Exposure to Rule Out Pulmonary Embolism in Pregnant Women


Pulmonary embolism (PE) is responsible for maternal death in approximately one of every 100,000 deliveries in Western countries. Diagnosing PE is problematic because characteristic symptoms such as shortness of breath and leg edema are common in normal pregnancy, and frequently used imaging tests such as computed tomographic pulmonary angiography (CTPA) expose mother and fetus to radiation. Algorithms using clinical prediction rules and blood testing for D-dimer level have been shown to reduce the need for CTPA in patients with suspected PE. However, the safety of this approach in pregnant women has not been confirmed.

Dr. Liselotte M. van der Pol and colleagues performed a multicenter, prospective cohort study that used the YEARS criteria (clinical signs of deep-vein thrombosis [DVT], hemoptysis, PE as the most likely diagnosis) and a D-dimer level to direct management of pregnant patients with new onset or worsening chest pain or dyspnea. Women who had none of the YEARS criteria plus a D-dimer level less than 1,000 ng/mL or one to three YEARS criteria plus a D-dimer level less than 500 ng/mL did not undergo CTPA, and anticoagulant therapy was withheld. Women with any other combination of results underwent a CTPA (or compression ultrasound for signs and symptoms consistent with DVT). The primary outcome measure was the proportion of women who had anticoagulant therapy withheld based on the algorithm who were diagnosed with symptomatic PE or DVT at 94 days.

A total of 498 pregnant women (mean age of 30 years), the majority in their third trimester (49%), were enrolled. Of 195 women who had PE ruled out based on the algorithm, one developed a DVT (YEARS 0, D-dimer 480 ng/mL, 2nd trimester) during follow-up, yielding a total missed venous thromboembolism (VTE) rate of 0.51 percent (95% CI, 0.09%-2.9%). Of the entire study population, PE was diagnosed in 3 percent, and DVT in 1 percent. CTPA was excluded using the algorithm in 39 percent of pregnant women without the need for CTPA.

In conclusion, PE was safely excluded using the algorithm in 39 percent of pregnant women without the need for CTPA. This study confirms the value of a diagnostic strategy that uses a validated clinical prediction rule to dictate the D-dimer threshold for excluding VTE. The premise of this approach is that a high D-dimer threshold is used in settings with low VTE prevalence (≤9%, YEARS = 0), whereas a lower D-dimer threshold is used when the prevalence is higher (YEARS = 1-3). Using either a clinical prediction rule or D-dimer testing alone is not as accurate and may partly explain the dissapoint results of another pregnancy-associated PE diagnostic study.

Limitations of this study include selection bias (all women had at least a moderate suspicion of PE) and the D-dimer level for some patients was known prior to (and may have influenced) determination of the YEARS score. It is also worthy of note that the subgroup with highest incidence of PE (first trimester) was also the smallest subgroup in terms of numbers (n=74), which resulted in an upper limit of the CI reaching 15 percent. This subgroup will need to be watched carefully as the study algorithm becomes more widely used. Overall, given the reduction in need for radiation exposure and the difficulties in conducting research in pregnant women, this study is a laudable accomplishment.

Disrupted Nuclear Export of Proteins Drives the Development of B-cell Malignancy


Putting of proteins between the nucleus and cytoplasm is a highly regulated process that is essential for normal cellular function. Aberrant nuclear export is frequently observed in blood cancers (e.g., cytoplasmic localization of mutant NF1 in acute myeloid leukemia), and novel mechanisms by which nuclear-cytoplasmic distribution of proteins might alter are of great interest. Export-1 (XPO1) is the major nuclear export receptor in all eukaryotic cells that functions through identification of nuclear export signals (NESs) in a sequence-specific manner, favoring the export of cargoes with NESs. Interestingly, most proteins only showed changes in one compartment without the expected reciprocal change; for example, a protein that increased in abundance in the cytoplasmic compartment in the presence of XPO1 mutation did not usually show reciprocal reduced expression in the nucleus. Presence of XPO1 mutation rendered cells sensitive to nuclear export inhibitors KPT-185 and the first-in-class selinexor (KPT-330), which was recently approved by the U.S. Food and Drug Administration.

In summary, Dr. Taylor and colleagues identified specific mutant residues in XPO1 that drive lymphoid malignancy, investigators carried out biochemical, structural, proteomic, and molecular studies, XPO1*E571K mutations were shown to alter nuclear export recognition in a sequence-specific manner, favoring the export of cargos with negatively charged nuclear export signals (NESs). This resulted in disruption of nuclear-cytoplasmic distribution of hundreds of proteins, including a number known to contribute to the oncogenic process. Importantly, most proteins only showed changes in one compartment without the expected reciprocal change; for example, a protein that increased in abundance in the cytoplasmic compartment in the presence of XPO1 mutation did not usually show reciprocal reduced expression in the nucleus. Presence of XPO1*E571K mutation rendered cells sensitive to nuclear export inhibitors KPT-185 and the first-in-class selinexor (KPT-330), which was recently approved by the U.S. Food and Drug Administration.

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Overall, this work highlights the complexity of MPNs and stresses the importance of the integration of multi-omics approaches to understand disease biology and to identify effective therapeutic targets. This article has generated a wealth of data adding to the growing number of resources readily available for hypothesis generation and testing, as well as validation of murine or in vitro models of disease, and will enhance the capability of the research community to target MPNs.


JASMINTH STRAUSSE, PHD, AND STEVEN LANE, MBBS, PHD, FRACP, FRCPA Dr. Strauss and Dr. Lane indicated no relevant conflicts of interest.
Multiple myeloma (MM) is a rare hematologic malignancy characterized by the clonal expansion of aberrant plasma cells within the bone marrow. MM is characterized by widespread intratumor heterogeneity and clonal evolution, which is believed to be the main driver of development of durable clinical responses (CRs). This is especially so in the case of the risk assessment of patients with MM, which are defined by an overall survival (OS) of two years or less despite the use of novel treatments.

Next-generation sequencing (NGS) analyses of MM and its precursor stages of monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM), has led to a profound understanding of the underlying disease biology and clonal evolution patterns in MM. Currently, the consensus for the classification of newly diagnosed MM (NDMM) includes molecular cytogenetics to risk stratify patients into high-risk, intermediate-risk, and low-risk groups, using the IMWG criteria. Patients with NDMM who are characterized by translocation of the immunoglobulin light chain (i[L]) light chain locus. Dr. Barwick’s team performed long-inset whole-genome sequencing analyses on a large cohort of patients with NDMM (n = 780). While NGS observed common translocations of the immunoglobulin heavy chain region with partner oncogenes, such as (11;14), (11;14), and (14;16), these were not predictive of patient prognosis. Notably, patients harboring t(11;14) accounted for approximately 10% of NDMM patients (n = 78/795) and were associated with poor progression-free survival (PFS), OS, and CR. While translocations occurred throughout the genome and were rare, i[L] MYC translocation was the most prevalent, accounting for 41% of patients (n = 32 of 78). Interestingly, i[L] translocations were found to be subclonal and were associated with hyperdiploidy, which is a remarkable marker associated with standard risk. However, patients harboring t(11;14) were found to have significantly worse PFS and OS rates compared to patients without t(11;14). Moreover, the hyperdiploid risk profile was performed on a subset of patients (n = 629) to determine if i[L] patients show an underlying gene expression signature or associated with MM subtypes; however, no specific relationship was found. Patients with an i[L] translocation were observed to have poor CR to immunomodulatory (IMiD) treatment. To investigate the underlying mechanism, chromosomal immunoprecipitation sequencing of ikaros family zinc finger 1 (IKZF1), a lymphoid transcription factor, led to the discovery of a comprehensive understanding of myeloma, which will allow tumors to be diagnosed, risk stratified, and treated based on intrinsic genetic factors. Indeed, the MMRF has recently launched the Myeloma Developing Regimes Using Advanced DRUGs (MDR-U) protocol clinical trial to test a pressing medical need for the development of approved and late-stage drugs in development that are untested in MM, which may be appropriate.

Notably, due to the nature of clonal evolution, in which subclonal populations continually evolve under selective pressures, a patient may acquire abnormalities in a subclonal branch during the continuum of disease that was not initially present at diagnosis. Therefore, current classification methods at diagnosis may not identify true risk status with the same degree of accuracy as genetic-based biomarkers. Indeed, large cohorts of patients with NDMM are important for the statistical power needed to identify both frequent and rare genomic abnormalities. This recognition underlies the Multiple Myeloma Research Foundation (MMRF)’s Clinical Outcomes in Multiple Myeloma to Personalized Assay (CoMMPass) study (ClinicalTrials.gov identifier: NCT01454297), which aims to collect samples from more than 1,000 patients from U.S. laboratories to create a reference database. In this case, they demonstrated that translocation of the immunoglobulin gene does not elegantly demonstrate how large patient cohort investigations can tease out critical infrequent genetic abnormalities. In this case, they demonstrated that translocation of the immunoglobulin light chain locus. Dr. Barwick’s team performed long-inset whole-genome sequencing analyses on a previously uncharacterized cohort of patients, which were characterized by translocation of the immunoglobulin light chain (IgL) light chain locus. In this way, we can gain an understanding of genetic characteristics, but also the role of noncoding, epigenetic, and tumor microenvironment changes that contribute to disease burden. Ultimately, a comprehensive understanding of MM will result in precision medicine approaches for early intervention and treatment strategies for what we strive to somehow cure a bedridden disease.

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5. Hypodiploid ALL is one of the most chemotherapy-refractory subtypes of B-ALL. Identifying a novel potentially efficacious therapy for B-ALL to select for therapies and exhibit a critical impact. Clinical trials focused on studying hypodiploid ALL are needed.
Is Hematology Having an Identity Crisis?


CLL-14 is a randomized phase III clinical trial designed for elderly patients with chronic lymphocytic leukemia (CLL) requiring first-line treatment. Eligible patients were assigned to either venetoclax-obinutuzumab (VO) or chlorambucil-obinutuzumab (CO). In both treatment arms, obinutuzumab was administered for six months, while venetoclax and chlorambucil were administered for a one-year fixed duration. The primary endpoint of the trial was progression-free survival (PFS), the median age of participating subjects was 72 years, with 216 patients randomized to each treatment arm. At the time of the report, the median follow-up was 28 months. The probability of remaining in remission at two years from study entry was 88 percent in the VO arm versus 64 percent in the CO arm (P<0.001). VO was also superior for overall response rates (90% vs. 71%), complete response rate (49% vs. 23%), and for minimal residual disease (MRD) negativity (94% with VO vs. 57% with CO). There was no difference in overall survival. VO performed well even in higher-risk subgroups such as those with unmutated IGHV genes and 17p deletions.

The management of first-line CLL has changed markedly in the past decade. Historically, the FCR (fludarabine, cyclophosphamide, and rituximab) regimen was recommended for the young healthy patients, the bendamustine-rituximab (BR) regimen for older patients, and chlorambucil-based treatment for the older and frail. Then in 2015, the BTK inhibitor ibrutinib received a frontline indication in CLL based on its superiority to chlorambucil (the ‘BR b walking’ of CLL management). The option of targeted oral therapy with a good adverse effect and safety profile is a major advance for managing CLL. However, randomized data suggesting superior outcomes over more potent options such as FCR and BR were lacking until just recently. When ibrutinib was shown to outperform both FCR and BR head-to-head in separate U.S. intergroup trials,10,11 Armed with these strong new data, ibrutinib has become the preferred frontline option for patients with CLL, both young and old. However, a vexing issue with ibrutinib as frontline therapy is the requirement for continuous and indefinite treatment. Long-term follow-up from frontline ibrutinib trials shows responses are maintained in more than 70 percent of patients at five years, but discontinuations due to toxicities can be 25 to 40 percent. For patients with low-grade but chronic toxicities, the cumulative effect can render impaired quality of life. Additionally, ibrutinib is expensive therapy, and the cost over time is substantial. With these pros and cons in mind, the overwhelming recommendation has a substantial interest in developing a time-limited, targeted therapy was to enhance treatment in two fields with substantial overlap. However, in the setting of diminished nonmalignant hematology faculty and resources, perceived and actual exposure to nonmalignant hematology is often dwarfed by overall emphasis on oncology-related curricula. In this respect, academic single-board hematology programs may increase retention of fellows within the hematologic disciplines by validating the field and increasing dedicated exposure to exclusive hematology training. Additionally, single-board hematology programs offer the possibility of a top-down recruitment effect by exposing medical students and resident trainees to hematology fellowships.

As part of its recruitment and retention efforts, we recently developed and administered a survey to U.S. hematology-oncology fellows to determine their attitudes and perceptions toward single-board hematology training. Of the 98 program directors who responded (65% response rate), the vast majority believed that single-board hematology training was both necessary and sufficient for fellows specializing in nonmalignant hematology. Furthermore, more than one-third of program directors reported that they would be interested in implementing a single-board hematology track at their own institutions if funding were available.

There are, however, several skeptics to this proposal to re-introduce single-board hematology programs. Since the Accreditation Council for Graduate Medical Education first recognized combined hematology-oncology fellowship programs in 2003, the number of single-board hematology programs has steadily declined. From a peak of approximately 160 hematology programs in the 1980s, there are now just three institutions that offer formalized hematology-only programs/tracks in the Electronic Residency Application Service. On our recent program director survey, the most common barrier to developing single-board hematology tracks was a concern about job availability for fellows.12 Our program director survey is that exposure to hematology patients, research experiences, and mentorship was associated with a decision to pursue a hematology-only career path. Additionally, the study found that trainees’ decisions to specialize in hematology or oncology were made along the entire spectrum of training, from medical school to residency to fellowship. Given these findings, the ASH Recruitment and Retention Working Group endorsed three primary recommendations to enhance recruitment of trainees into hematology: 1) to foster the development of single-board hematology training tracks in the United States; 2) to convene a national summit on mentorship, sponsored by ASH, to strengthen the impact of hematology mentorship among all levels of training; and 3) to expand the ASH Ambassador Program, a nationwide program consisting of ASH faculty “ambassadors” at different medical schools, to increase student and trainee recruitment into the field.

Of the workforce recommendations, the most drastic and provocative is the end of federal support for 70 fellowship tracks. ASH offers separate board examinations for adult hematology and medical oncology, yet the majority of fellows (134 participating programs) are structured as combined hematology-oncology training programs.13 Certainly, the original intent of combined training was to enhance treatment in two fields with substantial overlap. However, in the setting of diminished nonmalignant hematology faculty and resources, perceived and actual exposure to nonmalignant hematology is often dwarfed by overall emphasis on oncology-related curricula. In this respect, academic single-board hematology programs may increase retention of fellows within the hematologic disciplines by validating the field and increasing dedicated exposure to exclusive hematology training. Additionally, single-board hematology programs offer the possibility of a top-down recruitment effect by exposing medical students and resident trainees to hematology fellowships.

Hematology as a specialty is more than 125 years old; yet, despite our wisdom and history, we are training fewer academic hematologists in the United States. At a time when new therapeutics for sickle cell disease, hemophilia, and thrombosis are being developed at lightning speed, it is up to academic training programs to ensure that the U.S. workforce is to identify key factors affecting the hematology physician workforce and to assess the job market for new hematologists, with a particular focus on nonmalignant hematology. The first phase of the study, consisting of a survey of nearly 1,900 fellows in adult hematology-oncology programs throughout the United States, was completed in 2018 and has already revealed some concerning results. Of the 850 respondents (45% response rate), only 4 percent stated that they planned to pursue nonmalignant hematology as a primary career focus—a figure that has not changed at all since the 2003 ASH program director survey. That this number has remained stagnant throughout the past 15 years is alarming; however, it is more worrisome when taking into account the rapid pace of advances in the classical hematology disciplines of thrombosis, hemostasis, and hemoglobinopathies. In academics, where subspecialization in a specific disease type is the norm, a dwindling workforce in exclusive nonmalignant hematology could have far-reaching implications, ranging from decreased availability of expert care for nonmalignant diseases to diminished exposure to nonmalignant hematology for trainees. Even now, many academic institutions only have a small number of nonmalignant hematologists on faculty, often in predominantly clinical roles.

With the decades-long low accrual in nonmalignant hematology and a projected shortage of hematologists from top to bottom, the recruitment conundrum can seem like an insurmountable challenge. One of the primary findings from the fellow survey is that exposure to hematology patients, research experiences, and mentorship was associated with a decision to pursue a hematology-only career path. Additionally, the study found that trainees’ decisions to specialize in hematology or oncology were made along the entire spectrum of training, from medical school to residency to fellowship. Given these findings, the ASH Recruitment and Retention Working Group endorsed three primary recommendations to enhance recruitment of trainees into hematology: 1) to foster the development of single-board hematology training tracks in the United States; 2) to convene a national summit on mentorship, sponsored by ASH, to strengthen the impact of hematology mentorship among all levels of training; and 3) to expand the ASH Ambassador Program, a nationwide program consisting of ASH faculty “ambassadors” at different medical schools, to increase student and trainee recruitment into the field. Is Hematology Having an Identity Crisis? [Cont. from page 1]
assessments will be repeated. The primary objective of this prospectively for a year, at which time all baseline occlusive crisis (VOC) or acute chest syndrome episode who are not at “steady state,” defined as having a vaso-
receiving activated thromboplastin time, protein C, and protein S; polysomnography and the end of the first year of CPAP transfusion within two months, are currently pregnant, or apnea (OSA). This study will exclude individuals already SS genotype only) between age 15 years and three months prior to initiating study procedures.

Participants will undergo study procedures at baseline and at one-year follow-up. Frequency of VOC over the next year will be assessed prospectively as the primary outcome measure. Study procedures include a polysomnography examination to determine their apnea/hypopnea index (AHI) over oxygen saturation, blood samples, and various assessments to evaluate autonomic function and vascular reactivity. Participants with elevated AHI will be placed on continuous positive airway pressure (CPAP) and followed prospectively for a year, at which time all baseline assessments will be repeated. The primary objective of this trial is to determine the frequency of VOCs between first polysomnography and the end of the first year of CPAP treatment. Additional correlative studies will include analysis of hematologic markers including red blood cell (RBC) count, hemoglobin concentration, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin concentration, lactate dehydrogenase, bilirubin, and aspartate transaminase; hematopoietic parameters including blood viscosity measured by cone plate viscometer at several shear rates, RBC deformability measured by ektacytometry, and RBC aggregation properties measured by laser backscatter method; the inflammatory marker C-reactive protein; procoagulant markers including prothrombin time, D-dimer, fibrinogen, activated thromboplastin time, protein C, and protein S; and oxidative stress markers, namely advanced oxidation product proteins, malondialdehyde, super oxide dismutase, catalase, glutathione peroxidase, and ferric-reducing ability of plasma. An arterial blood gas assessment measuring oxygen and carbon dioxide pressure and pH will also be performed. Vascular function will be measured using a laser Doppler flowmeter to measure skin blood flow in resting condition and via a local hyperthermia test (LTH). The LTH evaluates vasodilation caused by axonal reflex and assesses the ability to produce enough nitric oxide to promote vasodilation. Autonomic nervous system activity will be evaluated using electrocardiographic signals acquired by the polysomnographic machine.

Rationale: The long-term negative impact of OSA on vascular and autonomic nervous system function has been well recognized, with increasing knowledge of its application and implications for individuals living with SCD. Comorbid OSA was identified among 21 percent of children with SCD in a retrospective study. These children had 47 percent more health complications and higher rates of complications per year than those without OSA. OSA was associated with intermittent dips of low oxygen levels during sleep, resulting in pulmonary, cardiovascular, neurological, and behavioral morbidities.6 OSA is highly prevalent (40-80% of patients) in the SCD population, however, there remains a gap in the research focusing on the association between OSA and SCD and its consequent impact on short- and long-term morbidity and mortality, particularly among adults. Several studies have reported the high prevalence rates of sleep disorders and OSA in adults and children with SCD; however, there is a paucity of research on how to mitigate the potential negative consequences of OSA in an individual living with SCD.

This study will explore the impact of CPAP on improving rates of VOC as well as various biologic parameters of disease severity in individuals with SCD and comorbid OSA. It will be blinded, randomized, and conducted at clinical centers in most of the United States. After informed consent, the number of VOCS requiring hospitalization in the previous two years will be abstracted from their medical records prior to initiating study procedures.

Sponsor: Hospices Civils de Lyon

ACCRUAL GOAL: 80 participants

PARTICIPATING CENTERS: Hôpital Édouard Herriot, Lyon, France (Giovanna Cannas); Centre Leon Berard, Lyon, France (Alexandra Gauthier); Hôpital de la Croix Rousse, Lyon, France (Emeric Stauffer)

Study Design: This is a prospective nonrandomized parallel assignment intervention trial. The trial will enroll individuals living with sickle cell disease (SCD; homozygous SS genotype only) between age 15 years and three months up to age 50 years and showing signs of obstructive sleep apnea (OSA). This study will exclude individuals already receiving treatment for OSA, those who have had a blood transfusion within two months, are currently pregnant, or who are not at “steady state,” defined as having a vaso-occlusive crisis (VOC) or acute chest syndrome episode within two months. After informed consent, the number of VOCS requiring hospitalization in the previous two years will be abstracted from their medical records prior to initiating study procedures.

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for advanced-stage HL differs with age, favoring chemotherapy with ABVD backbone with infrequent use of radiation therapy for adults, while in pediatric patients, COG has used a modified ABVD chemotherapy regimen of doxorubicin, bleomycin, and vincristine, plus etoposide, prednisone, and cyclophosphamide (ABVE-PC), with risk-adapted response-based use of radiotherapy (approximately 76% of pediatric patients receive radiation treatment). On SIOP, for the first time, adults and children will be treated with a uniform chemotherapy backbone regimen of AVD, with the addition of a monoclonal antibody and elimination of bleomycin. Radiation therapy may be used at the discretion of investigators under certain protocol-defined circumstances. Importantly, although HL is characteristically a disease of young patients (median age, 29 years), approximately 20 percent of patients with HL are older than 60 years.1 In older adults, response rates are lower, and toxicity is increased with ABVD, particularly the pulmonary toxicity associated with bleomycin. This trial provides an opportunity to allow for the outcomes of older adults with HL, and to explore the quality of life metrics in treating this vulnerable patient population. The randomized incorporation of novel agents into frontline therapy is for advanced HL is enthusiastically anticipated.


13. In this innovative work, the investigators demonstrate that osteoproliferin released by macrophages plays a key role in the chemotraction of neutrophils in transmigration-related acute lung injury, thus identifying a novel mechanism of transmigration-related death.


This article reports promising results of a new triple combination that includes carfilzomib and daratumumab for lenalidomide-refractory multiple myeloma.


This unique large-population study examines the prevalence of JAK2 V617F and calreticulin (CALR) mutations in the general population and suggests higher rates of subclinical myeloproliferative neoplasms in the general population associated with higher blood counts and increased thrombotic risk.


In a plenary paper, the authors present data in support of a role for patrolling monocytes in the clearance of sickle red blood cells (RBCs) from the microvascular endothelium and the inhibition of vaso-occlusion in sickle cell disease (SCD), a concept with potential for targeted therapy.

JULY 25, 2019


Dr. Michael A. Liu and colleagues demonstrate that gait speed is an excellent predictor of unplanned hospitalization, emergency department use, and mortality in adults at least 75 years of age who have a hematologic malignancy.

AUGUST 1, 2019


This study substantiates the role of the macrophage in the formation of erythrophagocytic islands (Ellis) and reveals that erythropoietin receptor (EpoR) expression marks the central macrophage of the SbH. Treatment with Epo increases the number of Ellis and erythroblasts surrounding the central macrophage.


This article reports promising results of a new combination that includes carfilzomib and daratumumab for lenalidomide-refractory multiple myeloma.

AUGUST 8, 2019


In a plenary paper, Dr. Rachel A. Bender Ignacio and colleagues describe a novel “serouservity” that detects immunoglobulin G responses to a wide range of viruses to characterize the reconstitution of the B-cell antiviral repertoire after allogeneic stem cell transplantation.


Dr. Kamran Bakhitiari and Joost C. M. Meijers report that some factor IX concentrates increase thrombin generation in vitro in patients with factor XI deficiency and that this results from low-level contamination with factor IXa. If confirmed in vivo, this has potential implications for the treatment of factor XI deficiency.

AUGUST 15, 2019


In a plenary paper, the authors present data in support of a role for patrolling monocytes in the clearance of sickle red blood cells (RBCs) from the microvascular endothelium and the inhibition of vaso-occlusion in sickle cell disease (SCD), a concept with potential for targeted therapy.
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.¹²

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.

* 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.