BRAD KAHL, MD

Whether one opts to use it in just sALCL or more broadly, it is clear we did receive broad FDA approval for use in any CD30 study is required to prove the benefit in these subtypes. However, BV I find the data in PTCL-NOS and AITL unconvincing and believe more my opinion, no. I would definitely add BV to manage any case of sALCL.

In another way, the three-year PFS for A+CHP was 57.1 percent, versus 44.4 percent for CHOP. A+CHP was also superior for overall survival with a hazard ratio of 0.66 (p=0.024). Rates of adverse events were similar between groups. Febrile neutropenia was seen in 18 percent of A+CHP patients and in 15 percent of the CHOP group, and peripheral neuropathy was observed in 52 percent and 55 percent of these patients, respectively.

Outcomes for patients with aggressive T-cell lymphomas have remained frustratingly inferior to those of their B-cell counterparts. There has been no rituximab equivalent to close the gap. However, with the completion of the ESCHELON-2 trial, it seems the gap will finally narrow for a subset of patients with T-cell lymphoma. In ESCHELON-2, 70 percent of patients enrolled had systemic aggressive large cell lymphoma (sALCL), a T cell lymphoma defined by high expression of CD30. The benefit observed in the trial was large in this group of patients and seems to have driven the overall results. For patients with the much more common entity of PTCL-NOS and the less common entity of angioimmunoblastic T-cell lymphoma (AITL), which tend to have weak expression of CD30, there was no statistically significant benefit for PFS.

In the trial, CD30+ was defined as more than 10 percent of cells by local review. Any case of sALCL will easily meet that threshold. Perhaps 50 to 60 percent of your PTCL-NOS and AITL will meet that threshold. So, should you use BV to treat any T-cell lymphoma with CD30+ features? In my opinion, no. I would definitely add BV to manage any case of sALCL. I find the data in PTCL-NOS and AITL unconvincing and believe more study is required to prove the benefit in these subtypes. However, BV did receive broad FDA approval for use in any CD30+ T-cell lymphoma.

Whether one opts to use it in just sALCL or more broadly, it is clear we have achieved a major therapeutic advance in the front line management of some T-cell lymphomas.
In the Interest of Transparency

Recent high-profile stories in the lay press, including front page feature articles in the New York Times, have again placed the issue of conflicts of interest (COIs) in medical science, particularly malignant hematology drug development, in the public sphere. Obvious COIs are clear threats to the trust that patients, elected officials, and the general public place in the medical profession. We as hematologists have the focus to keep these type of COIs in line with the strictest restrictions that owners of intellectual property can have in the execution and reporting of clinical trials related to that property. More insidious is the threat to public and scientific community trust, engendered by the more subtle and difficult-to-delineate concepts of "potential" COI or "appearance" of COI. When leaders of our most prominent clinical cancer research centers serve as highly compensated members of pharmaceutical company boards, or when investigators leading clinical trials of agents owned by companies also serve as highly compensated members of speakers panels or scientific advisory boards for these companies, our well-deserved public trust risks erosion. The purpose of this column, of course, is that the academic thought leaders invited to serve in these compensated roles may well be the most qualified individuals to provide company boards with sage advice that ultimately will serve our patients well. The challenge to our profession is thus to balance the risk to public trust with the benefit of providing our expertise to accelerate translational research; and the question we must confront is whether simply disclosing these relationships is sufficient to eliminate the potential COIs.

Every academic institution must develop its own approach to these issues, but ASH, as a professional society representing more than 17,000 scientists and clinicians, has led by example in this complex environment. We have rigorous, thoughtful, and transparent policies to manage potential COIs, whether they be financial, institutional, or personal. Every ASH volunteer is required to disclose potentially relevant financial interests, and every committee, study section, task force, working group, and editorial board has a COI officer who is charged with reviewing these disclosures and ensuring that potential conflicts are addressed. At all meetings of these groups, the COI officer reviews ASH COI policies as the first agenda item of the meeting, and members are instructed to participate in managing potential conflicts and to be diligent in paying attention to potential conflicts. Members in conflict recuse themselves from relevant discussions and decisions. These policies have special relevance to ongoing ASH efforts in developing evidence-based clinical practice guidelines. ASH has developed clear and transparent disclosure requirements for all scientific meetings and publications, as well as oversight processes to ensure that our policies are followed, including empowering session moderators at the ASH annual meeting to call out potential COIs not disclosed by presenters. Rarely, undisclosed conflicts are discovered after articles are published, and we have clear policies that allow ASH leaders to authorize our journal editors to retract abstracts and publications, based solely on violation of COI policies.

Managing COIs is an important and difficult challenge. Ethicists debate whether participation in the for-profit pharmaceutical marketplace by clinical investigators is manageable by disclosure and recusal. ASH policies support this approach, but we recognize that implicit biases rooted in personal relationships, life experiences, and professional networks color our thinking in ways that are much more difficult to manage. We are committed to keeping the COI issue front and center in all our activities and welcome input from our members on this topic.

Sir David Weatherall, MD, FRCP, FRS (1933 - 2018)

My dear colleague, Regius Professor Sir David J. Weatherall, MD, FRCP, FRS, founder of the Weatherall Institute of Molecular Medicine, and recipient of the Lasker-Koshland Award for Special Achievement in Medical Science and the Waldee G. Crumley Award for Lifetime Achievement in Hematology, died on December 8, 2018, at age 85 following a daunting fall.

David leaves his lovely wife Stellas; his fine son Mark, an excellent neurologist; and his five grandchildren, Lauren, Monty, Theo, Raphael, and Sebastian. He also leaves his most powerful heritage, the outstanding Dr. Doug Higgs, and scores of other trainees whose contributions amplify his remarkable achievements. He is deeply mourned by all of them and by his loyal assistant Liz Rose, his colleague in international hemoglobinopathy management Dr. Nancy Olivier, and by the community of hemoglobinopathy scholars of which he was the leader.

I have been a close friend and deep admirer of David since the early 1980s when he was at Johns Hopkins working with the estimable Dr. John Ogg on a method to separate the alpha from non-alpha chains of hemoglobin. I, too, had seen my first case of thalassemia in the late 1950s and was filled with curiosity. David’s inquiries, together with the pioneering and clinical diagnostical laboratory studies of Drs. Ruggero Crippelli, Marcello Siniscalco, and Phaedon Fessas were my guiding lights.

Dr. Weatherall and Nathan (L to R) at Christchurch College, Oxford, UK, on the occasion of Dr. Weatherall’s retirement (September 2000). At the event, the Chancellor of Oxford University thanked Dr. Weatherall for 25 years of service and in his honor, renamed the Institute of Molecular Medicine the Weatherall Institute of Molecular Medicine.

In demise and later in many others, David Weatherall was a nonpareil friend. I will forever treasure his memory. So will hematology.

– David G. Nathan, MD
President Emeritus, Dana-Farber Cancer Institute, Physician-in-Chief Emeritus, Boston Children’s Hospital, Professor of Pediatrics and Medicine, Robert A. Stranahan Distinguished Professor of Pediatrics and the Richard A. Smith Distinguished Professor of Medicine, Harvard Medical School
Upcoming ASH Awards Deadlines

ASH is committed to supporting hematologists at all stages of their careers and thus provides an array of awards and programs to help them advance in the field of hematology. Several application deadlines are coming up; make sure to check the ASH website for additional information.

- The Harold Amos Medical Faculty Development Program (ASH-AMFDP), part of the Minority Recruitment Initiative, provides four years of research support, including an annual stipend of up to $75,000 and an annual grant of $30,000 to support research activities for underrepresented minority scholars in hematology. Apply by March 19, 2019, via www.hematology.org/ASH-AMFDP.

- The ASH Clinical Research Training Institute (CRTI) is a yearlong education and mentoring program for hematology fellows and junior faculty at academic medical centers. CRTI participants will have the opportunity to learn about clinical research methods, research collaborations, statistical analysis, and managing the demands of family and career. For more information and to apply by the deadline of March 29, 2019, visit www.hematology.org/CRTI.

- The ASH Medical Educators Institute (MEI) offers a “bootcamp” in teaching techniques, medical education scholarship, and career development for hematologists and fellows starting medical education careers. For application requirements and to apply by the deadline of March 31, 2019, visit www.hematology.org/MEI.

- The ASH Visitor Training Program (VTP) provides funding for hematologists or hematology-related health care professionals in the developing world to receive training on a specific topic for up to 12 weeks, in an effort to help build hematology capacity in developing countries. Apply by April 5, 2019, by visiting www.hematology.org/VTP.

- The ASH Global Research Award is designed to support future international scientific leaders, increase hematology capacity, and nurture global collaborations. For further details and application information, visit www.hematology.org/Global-Research. Submit your application by April 15, 2019.

- The ASH Bridge Grant helps hematologists continue their research amidst National Institutes of Health (NIH) funding reductions. A $150,000 award is granted to an ASH member who applied for an NIH R01 or equivalent grant but was denied funding due to budget cutbacks. ASH grants approximately 20 to 30 one-year awards each year. For additional information and to apply by May 1, 2019, visit www.hematology.org/BridgeGrants.

There Is Still Time to Attend the 2019 International Highlights of ASH

There is still time to register and attend a 2019 Highlights of ASH meeting. Attendees will obtain a synopsis of the top hematology research presented at the latest ASH annual meeting and learn ways to improve patient management and care strategies from internationally acclaimed experts. The meetings also provide an opportunity to network with top minds in the field and a great educational experience for hematologists, oncologists, fellows and trainees, allied health professionals, and hematopathologists alike. Highlights of ASH in the Mediterranean, brought to you by The Athenaeum Inter-Continental Athens in Athens, Greece, Highlights of ASH in Latin America will take place April 5-6, 2019, at the Westin Lima Hotel and Convention Center in Lima, Peru. For additional information and to register, visit www.hematology.org/Highlights.

ASH News Daily Call for Authors

ASH is searching for the next team of authors for the 2019 ASH News Daily. If you are an ASH member (MD or PhD) who has a passion for writing as great as your love for hematology, you may just be the right fit. Ideal candidates are proficient, published writers who are curious about, and willing to cover, areas outside their comfort zone. You must be able to attend the annual meeting in December as well as an in-person editorial board meeting in late September.

We are also seeking those who:
- Have a flexible schedule at the annual meeting and have strong time management skills
- Enjoy science writing and can also apply a creative approach to it
- Are cognizant of timelines and dependable with schedules and firm deadlines
- Enjoy networking and doing author outreach
- Are mid-career professionals interested in becoming more involved with ASH.

If this sounds like you or a colleague you wish to nominate, please email Managing Editor Juana Llorens (jllorens@hematology.org).

Required materials include a letter of interest, two writing samples, and a CV, due June 15, 2019. For more information on ASH News Daily, visit www.hematology.org/Annual-meeting/AND.aspx.

Maintenance of Certification ABMS Update

ASH submitted feedback on draft recommendations for reforming Maintenance of Certification (MOC) to a commission appointed by the American Board of Medical Specialties (ABMS) and other entities. ASH President Dr. Roy Silverstein commented,

“For four years, ASH has eagerly sought opportunities to work with ABMS to make meaningful changes to MOC that would better align with the needs of hematologists. The formation of the commission and its draft recommendations is the latest positive step taken by ABMS to take a long overdue look at MOC and to involve subspecialties in setting the course for change.”

Dr. Silverstein pointed out concerns over the summative test required periodically to pass certification. ASH is not a proponent of such tests as the Society believes that a single exam or assessment does not recognize the diversification of career paths in hematology and that testing without making continuing education resources available does not provide the tools necessary to improve knowledge and care.

ASH also hopes the Commission will reconsider its recommendation to reinstate the reporting of practice improvement activities as part of continuous certification. Read the ASH press release (www.hematology.org/Newsroom/Press-Releases/2018/9337.aspx) for more information and additional comments from Dr. Silverstein.
Transplantation and Myelofibrosis: A Little Medicine and a Little Art

TANIA JAIN, MBBS,1 AND JEANNE PALMER, MD2
1. Adult Bone Marrow Transplantation Service, Memorial Sloan Kettering Cancer Center, New York, NY
2. Division of Hematology and Medical Oncology, Mayo Clinic, Phoenix, AZ

Allogeneic stem cell transplantation (HCT) has established the potential to induce molecular and morphological remissions in patients with myelofibrosis. However, there have always been unique concerns with transplantation. Unlike, for example, patients with acute leukemia, patients with myelofibrosis, historically, have had higher toxicities from HCT, possibly due to splenomegaly, narrow fibrosis, or debilitating from the disease. These are in addition to the classical toxicities of the procedure, including organ damage from the conditioning regimen, graft-versus-host disease, relapse, and graft failure. To weigh the “risk versus benefit” balance in favor of benefit to patients, it becomes imperative to identify the right patient at the right time in the disease course to consider them for HCT. Adding another layer of thinking to this decision-making process is the advent of nontransplantation options such as JAK inhibitors and others in the pipeline that improve symptoms and, arguably, improve survival.1,2 Thus far, no comparative randomized data exist between HCT and nontransplantation therapeutic options to assess the magnitude of benefit of HCT in these patients. Hence, most decisions about HCT and the timing thereof are derived by logical extrapolation from available retrospective and registry data.

Disease Factors
Myelofibrosis is a chronic malignancy, the morbidity of which typically evolves over years. For the past decade, decision making for HCT often has been based on two scoring systems: the Dynamic International Prognostic Scoring System (DIPS) and the DIPSS-Plus. These prognostic metrics were developed to track risk profile over time.3,4 They have also helped establish the timeline for HCT in patients with myelofibrosis. An expert panel recommends consideration of HCT for patients younger than 70 years if they have refractory/transfusion-dependent anemia, peripheral blasts higher than 2 percent, or adverse cytogenetics, mainly derived from the poor median overall survival of five or fewer years.

Characteristic

<table>
<thead>
<tr>
<th>Patient</th>
<th>Transplant?</th>
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<tbody>
<tr>
<td>Age &lt; 65-70 years, good performance status, no/minimal comorbidities</td>
<td>Yes, considering disease factors</td>
</tr>
<tr>
<td>Age &gt; 70 years, good performance status, no/minimal comorbidities</td>
<td>Individualized evaluation considering disease/donor factors; recommend reduced intensity conditioning</td>
</tr>
<tr>
<td>Age &lt; 65 years, poor performance status, or comorbidities</td>
<td>Individualized decision considering disease/donor factors</td>
</tr>
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<thead>
<tr>
<th>Disease</th>
<th>Transplant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIPS/DIPSS Plus score = intermediate-2 or high</td>
<td>Yes, considering patient factors</td>
</tr>
<tr>
<td>DIPS score = intermediate-1, age &lt; 65 years, high risk cytogenetics, or molecular mutations (JH1/2, SRSF2, SF3B1 in primary or post-PV or post-ET and EZH2, ASXL1 in primary MF), or peripheral blood blasts &gt;2% or transfusion refractory anemia</td>
<td>Yes, considering patient factors</td>
</tr>
<tr>
<td>MIPSS70 Plus high risk very-high risk</td>
<td>Yes, considering patient factors</td>
</tr>
<tr>
<td>MIPSS70 Plus version 2.0 high/very-high risk</td>
<td>Yes, considering patient factors</td>
</tr>
<tr>
<td>MIPSS70 Plus/ MIPSS70 Plus version 2.0 intermediate risk with worsening clinical features</td>
<td>Yes, considering patient factors</td>
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<tr>
<th>Donor availability</th>
<th>Transplant?</th>
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</thead>
<tbody>
<tr>
<td>HLA matched related or unrelated donor</td>
<td>Yes, considering patient and disease factors</td>
</tr>
<tr>
<td>HLA haploidentical family member or umbilical cord blood</td>
<td>Individualized decision considering patient and disease factors</td>
</tr>
</tbody>
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Abbreviations: DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; HLA, human leukocyte antigen; MF, myelofibrosis; MIPSS, Mutation-Enhanced International Prognostic Score System; PV, polycythemia vera.

What Lies Ahead?
As illustrated in this article, while expert panel recommendations have been established, many aspects related to timing and the point of maximal benefit remain shrouded in the “no data zone.” Additionally, myelofibrosis being a relatively uncommon malignancy, it is almost obligatory to conduct collaborative efforts.

Transplantation versus nontransplantation options. Most established recommendations are based on the data available from the pre–JAK inhibitor era. Whether the same holds true with improvements attributed to JAK inhibitors remains a question. A randomized study to compare HCT versus non-HCT options would be difficult to conduct.
However, a current Center for International Blood and Marrow Transplant Research (CIBMTR) study of patients older than 55 years, to compare outcomes of patients undergoing HCT with those of an age-matched historical cohort (NCT02534477), which would shed some light toward this.

While on ruxolitinib. In real-world clinical scenarios, another challenging question is what is the best window to HCT when patients have improvement in symptoms while on JAK inhibitors. Is it when patients have the maximal response from JAK inhibitors or when they begin to lose the clinical response, such as at the return of the constitutional symptoms or splenomegaly? This can be feasibly studied in a randomized fashion as a collaborative effort.

Should you transplant if there are too many mutations? It also remains unknown whether the high risk portended by mutation status is overcome by HCT — information that can provide additional insight into identifying patients who may benefit from HCT considering that an early course in the disease (or not) and that might offer a benefit from HCT in these patients.

These are unprecedented times for cancer treatment. Only the most prescient among us might have predicted that in 2019 routine clinical practice could include the genetic modification of a patient’s own cells being used against acute leukemia, lymphoma, and many other cancers. And yet, that is here. The rapid availability of these living drugs, which includes T cells expressing chimeric antigen receptors (CAR T-cells), is a result of significant potential to control malignancies in patients who have failed other therapies. The U.S. Food and Drug Administration (FDA) has approved these drugs given a high efficacy signal but raised concerns regarding attending physicians, many of whom are not directly involved in treatment of pediatric acute lymphocytic leukemia (ALL), and tisagenleucel and axicabtagene ciloleucel for treatment of non-Hodgkin lymphoma (NHL), came with significant strings attached. Like any genetically engineered product using viral vectors, the FDA required that recipients of commercial CAR T-cells be observed for 15 years.1,2 Additionally, the FDA has implemented product development and evaluation and mitigation strategy (REMS) programs to maximize safety.3,4 These requirements are unprecedented for any drug approval to date and give us the opportunity to develop paradigms for measuring safety and efficacy over time in a rigorous and coherent manner.

With this mission in mind, the Center for International Blood and Marrow Transplant Research (CIBMTR), a decades-old outcomes database for hematopoietic cell transplantation (HCT), has expanded its infrastructure to capture data on cellular immunotherapies. The aim is comprehensive data collection through a standardized approach that can be used for both regulatory requirements and research. The recent implementation of the National Cancer Institute–funded Moonshot Initiative program called the Cellular Immunotherapy Data Resource, awarded to the CIBMTR, will further expand the CIBMTR’s infrastructure for real-world data on recipients of these cellular therapies.

The CIBMTR is a research collaboration between Medical College of Wisconsin and the National Marrow Donor Program/Be the Match that operates an outcomes database on HCT and now, cellular therapies. The operations of this nonprofit organization are funded primarily by federal grants. The CIBMTR also holds a contract with the Health Resources and Service Administration to operate the Stem Cell Therapeutics Outcomes Database (SCTOD) of the C.W. Bill Young Cell Transplantation Program. Through the SCTOD, according to the requirements of this contract, the CIBMTR functions as a public health authority to capture all allogeneic HCT performed in the United States, and analyze data to assess patient survival and center performance. The CIBMTR is a resource to the community, used for research in clinical outcomes, immunobiology, health services research, bioinformatics, statistical methodology, and clinical trials. This resource has resulted in more than 350 publications. An executive summary was released in August 2018, outlining the operations of this database over the past 10 years, highlighting both the productivity of the CIBMTR and its collaborative nature.

In the past three years, the CIBMTR has expanded its infrastructure to capture data on indications and outcomes of cellular therapies. The objective is to capture any cellular therapy, which is ever increasing and for long-term follow-up. The long-term follow-up approach of the cellular therapy registry intentionally aligns with FDA regulatory requirements that all cellular therapy products must be followed up on for at least 15 years to assess the risk of development of subsequent neoplastic conditions. CIBMTR also aligns with practices in the HCT field facilitated by the SCTOD throughout the past 40 years, where data collection is part of the culture and sheds light on real-world outcomes of patients who received transplantation.

Since the release of the cellular therapy outcomes database in 2016, this ongoing collaboration with the community has contributed to the ability to implement data collection practices and to test data collection forms at participating centers. The FDA approvals for both CAR T-cell products carry a requirement that manufacturers establish mechanisms for long-term follow-up of these patients. The CIBMTR is currently contracted with both Novartis and Kite/Gilead to use its cellular therapy registry database to capture data on outcome and adverse events. CIBMTR recently facilitated patients 60 years of age and older to fulfill these regulatory requirements. Notably, after these data are collected and reported to the relevant regulatory agencies, they will be available for research purposes following the pattern established with HCT data and the SCTOD. Additionally, in October 2018, the CIBMTR was awarded the Cellular Immunotherapy Data Resource program, whose main objective is to build and maintain an infrastructure for data collection from recipients of cellular therapies for cancer and implement data sharing practices to maximize the use of this data for research. The CIBMTR Cellular Therapy Registry is fully functional, with more than 80 centers in the U.S. currently reporting data.

Participation in the CIBMTR database is open to any program and requires establishing an agreement governing the terms and expectations of data and sample sharing, data completeness and quality, Institutional Review Board and Privacy Rule oversight, and use of the electronic data collection system. Data quality is a very high priority. CIBMTR performs regular data audits and assesses toxicities systematically through the CIBMTR Cellular Therapy Registry and subsequently share reports with each pharmaceutical company for submission to the FDA for review. This could be appropriately done for expected CAR T-cell–associated toxicities that are already included in the forms. If successful, this approach will serve as another important point of synergy and utilization of this registry and facilitate standardized capture of toxicities related to these therapies.

Another challenge in the field has been capturing toxicity in a uniform way with several different grant systems being issued by different investigators and industry. In parallel

Pulmonary Embolism Response Teams

(Cont. from page 1)

increased knowledge of high-risk PE pathophysiology and the perception that a multidisciplinary team improves care of patients. 6–8 The presence of a PERT may also further the education of attending physicians and residents and provide an infrastructure to capture data on cellular immunotherapies. Similarly, many interventionalists may be unfamiliar with all the new and emerging anticoagulant options. PERT assessment of patients with PEs of submassive or worse severity demands that the interventionalists consider the patients candidacy for invasive interventions such as CDT or IVC placement, as well as determine the type, duration, and intensity of anticoagulation. Furthermore, it remains unknown whether newer targeted oral anticoagulants are equally effective in circumstances in which patients have experienced a PE (e.g., after thrombectomy or with intracaval stents), thromboembolic pulmonary hypertension, or lupus anticoagulant–associated venous thromboembolism). Thus, as each PERT matures, these same issues should be evaluated on a broader scale and may be included in the PERT consensus or in local clinical pathways. These repeated processes ensure that PERT members are aware of the adverse events associated with these types of interventional devices and anticoagulants available at each institution. The establishment of a formal consensus by a PERT provides a framework to examine the sequences of each step of a clinical pathway to be periodically assessed and for the pathway to be appropriately modified.

The relative new appearance of PERTs in the medical landscape provides fertile ground for disseminating information and applying new techniques both faster and more appropriately at medical institutions of various sizes and missions. The relative uniformity of their design and implementation is expected to generate a valuable data gathering and performance of prospective research regarding innovative devices and other medical interventions. A few reports from institutions currently detail the potential value of PERT, including the first 3-month experience from MGH that found that the PERT paradigm was rapidly adopted, with the number of activations increasing 16 percent every six months.9,10 Reports from Cleveland Clinic and New York University similarly demonstrated that a multidisciplinary approach to cases of intermediate- and high-risk PE can be implemented successfully and that activations increased over time.11,12 These studies also suggest that PERT facilitates access to advanced therapies. A recent interrupted time-series analysis of the UCSD PERT found that the proportion of PE patients undergoing any advanced therapy, from 9 percent to 19 percent, after the introduction of a PERT.13 This increase was attributed largely to greater use of CDT, which grew from 1 percent to 14 percent. Importantly, even with an increase in advanced therapies following the implementation of a PERT, this analysis suggested a downtrend in both bleeding and mortality.14 More research is needed to confirm the effectiveness of PERT’s and, in particular, to determine if PERTs and the therapies they recommend improve clinical outcomes. Additionally, the benefits and effectiveness of PERTs regarding cost and patient quality of life need further investigation.

In 2015, a small number of these multidisciplinary teams convened to Boston to form the National PERT Consortium (www.pertconsortium.org) to advance the diagnosis, treatment, and outcomes of patients with PE. Since then, the consortium has gained members from Europe, China, Saudi Arabia, and South Africa, with more than 75 institutions and more than 1,500 members joining. Its vision is to guide and influence PE care worldwide through education, research and development, and to create a forum for various institutions to exchange views, educate, develop and disseminate evidence-based recommendations for patients with PE. The PERT Consortium has created a forum for various institutions to exchange views, educate, develop and disseminate evidence-based recommendations for patients with PE. The PERT Consortium provides a forum for various institutions to exchange views, educate, and set up treatment guidelines and protocols. If you are interested in learning more about establishing a PERT at your institution or joining the PERT Consortium, please visit www.pert consortium.org.

Government Affairs Committee Chair Speaks on the Need for Advocacy in the New Congress

ASH’s advocacy on Capitol Hill has continued briskly since the start of the 116th Congress. In January 2019, ASH’s government affairs staff visited the offices of all 39 incoming members of Congress to welcome them to Washington, and on March 7, the ASH Committee on Government Affairs visited more than 40 congressional offices. Committee members advocated for increased funding for the National Institutes of Health (NIH) and funding for sickle cell disease (SCD) data collection within the Centers for Disease Control and Prevention (CDC) for fiscal year 2020.

To learn more about ASH’s advocacy efforts, The Hematologist spoke with the Chair of the ASH Committee on Government Affairs, Dr. Alan Rosmarin. Dr. Rosmarin has been involved with ASH advocacy for more than a decade and has served as committee chair since 2017. “My involvement with the committee grew out of a lifelong interest in politics and the legislative process,” said Dr. Rosmarin. “The committee amplifies our voices in advocating for what matters most to us as physicians and scientists.”

Visiting legislators in Washington, DC, is a key component of the Society’s advocacy efforts. ASH organizes three major “Hill days” per year, which provide an opportunity for ASH members who are visiting Washington to meet with elected officials. “Being active with the committee on the state and national levels allows us to expand our influence as citizens, beyond what we can accomplish by talking with family, neighbors, colleagues, and others in our hometowns,” emphasized Dr. Rosmarin.

The Committee on Government Affairs also works to influence federal policy in other ways such as crafting policy statements and assisting with feedback for comments on proposed federal rule changes affecting hematologists. “The committee has an important voice in shaping ASH’s legislative and policy priorities,” said Dr. Rosmarin. “As Committee members, we are privileged to receive updates from leaders at NIH, CDC, and other federal agencies, and we benefit from the expertise and hard work of ASH staff.”

Thanks to the efforts of members of the Committee on Government Affairs, as well as ASH’s Executive Committee, Committee on Practice, and Grassroots Network, ASH has achieved numerous important advocacy victories in the past several years. ASH’s advocacy efforts in 2018 culminated with The Sickle Cell Disease and Other Heritable Blood Disorders Research, Surveillance, Prevention, and Treatment Act (S. 2465) being signed into law. This bill reauthorizes SCD prevention and treatment grants awarded by the Health Resources and Services Administration (HRSA) and authorizes the federal government to award data collection grants via the CDC. Dr. Rosmarin is particularly proud of ASH’s role in crafting the legislation. “Legislators, their aides, and the lay public look to us as experts in our fields who can provide real-world knowledge and experience.” ASH worked closely with both Senators Tim Scott (R-SC) and Cory Booker (D-NJ) to bring these efforts to fruition.

Dr. Rosmarin outlined several priorities for ASH’s advocacy efforts in the coming year, including continued work to ensure sustained funding for NIH, to advance SCD research and treatment, to promote palliative care, and to combat the opioid epidemic in a way that recognizes the unique needs of all patients. “It is remarkably gratifying to advocate for hematology, especially in these challenging times,” he said.

Dr. Rosmarin underscored how easy and fun it is to get involved in ASH’s advocacy efforts. “Even after nearly a decade on this committee,” he remarked, “I still feel like I’m on a class trip to Washington as I walk past the nameplates outside the offices of our senators and representatives.”

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

ASH members also can participate in the ASH Advocacy Leadership Institute, a two-day educational seminar that sends ASH members to meet with their representatives to advocate for hematology in Washington, DC, or apply to become an ASH Congressional Fellow and spend a year working in a congressional office. “Regardless of how we choose to participate, each of us has a responsibility to be an advocate for the good of patients, science, and the practice of hematology,” said Dr. Rosmarin. “Advocacy cannot be outsourced.”

Dr. Alan Rosmarin
Mixed-phenotype acute leukemia (MPAL) is defined by a blast population that expresses a specific combination of lineage-defining myeloid antigens and lineage-defining T- or B-lymphoid antigens. Through the 2008 WHO classification system, MPAL is categorized based on specific chromosome rearrangements involving BCR-ABL1 fusion and KMT2A (also known as MLL), but since the genetic basis of most cases of MPAL is unknown, most cases are classified as one of the following lineage mixes: B/myeloid MPAL, T/myeloid MPAL, or MPAL NOS. MPAL, which accounts for approximately 3 percent of acute leukemia cases in children and adults, is associated with a greater propensity for intrinsic resistance to chemotherapy and thus, has a poor prognosis. Because most patients with MPAL are excluded from all acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL) frontline clinical trials, the optimal treatment for MPAL remains uncertain. Retrospective analyses indicate that the outcomes for patients with MPAL are better when ALL-based chemotherapy regimens are used, but inferior to outcomes for equivalent pediatric or adult ALL and AML cohorts. Allelic hematopoietic stem cell transplantation (HSCT) in first remission improves outcomes and is recommended for patients with MPAL. Recent efforts have applied comprehensive genomic tools to MPAL to better understand its biology and provide insight as to why current therapies are less effective, as well as to develop better therapies for this group of poorly responsive patients with acute leukemia.

To this end, four reports published in 2018 have sought to characterize the genetics underlying MPAL. An international collaboration of pediatric MPAL cases stands out and is reported by Dr. Thomas B. Alexander and colleagues in Nature. The authors present the results of their comprehensive genomic analyses of pediatric MPAL and compare its “genomic landscape” to other pediatric acute leukemia subtypes. Additionally, they used cell sorting coupled with targeted sequencing to characterize the cell of origin for pediatric MPAL.

The authors analyzed 115 samples from patients with MPAL (T/M MPAL [n=49], B/M MPAL [n=33], KMT2A-MPAL [n=18], BCR-ABL1-MPAL [n=2]), MPAL NOS [n=8], and acute undifferentiated leukemia [n=3]) by whole exome or whole genome sequencing, transcriptome sequencing, single-nucleotide polymorphism array analysis, and methylation array analysis. The comparison cohorts included pediatric patients with AML, early T-cell precursor (ETP) - ALL, non-ETP T-ALL, and B-ALL.

They identified 158 recurrently altered genes with 81 genes identified in at least three cases. The most commonly mutated genes identified in pediatric MPAL are also commonly mutated in AML (FLT3, RUNX1, and CEBPA) and ALL (CDK20A, CDK20B, ETV6, and VPREB1), or both (WT1, KMT2A). Similar to studies of AML and ALL, KMT2A cases demonstrated the lowest mutation burden, and the mutation burden for T/M MPAL and B/M MPAL was similar to that of AML and ALL. Alterations in genes encoding transcriptional regulators were detected in the majority of T/M MPAL and B/M MPAL cases, with alterations in WT1, RUNX1, and CEBPA mainly occurring in T/M MPAL compared to ZNF384, VPREB1, TCF3, and PAX5 in B/M MPAL. Alterations in signaling pathway genes were common in all subsets with mutations in FLT3 being the most common signaling mutation and occurring in all subsets, but more frequently in T/M MPAL. Other mutations in signaling pathways such as N Ras and KRAS were distributed across all MPAL subsets. Mutations in genes encoding epigenetic regulators occurred in 69 percent of T/M MPAL cases and 63 percent of B/M MPAL. For KMT2A cases, in addition to translocation involving KMT2A, mutations in MIL7A and AFF1 were identified in more than one case.

A recurrent translocation involving the entire coding region of ZNF384 was present in nearly half the cases of B/M MPAL and in one KMT2A MPAL case. The genomic landscape and the gene expression profiles of ZNF384-associated B/M MPAL were similar to that of ZNF384-associated B-ALL except for KDM6A alterations, which were only identified in the MPAL cases. The authors propose that ZNF384 rearrangements define a distinct subtype of MPAL for consideration in future studies.

Genomic comparison studies were performed on cases of T-cell ALL, T/M MPAL, ETP-ALL, and AML. The authors found that core transcription factors known to drive TALL (TALI, TAL2, TLX1, TLX3, LMO1, LMO2, NKX21, HOX10, and MYL1) were less frequently altered in T/M MPAL and ETP-ALL, while genetic alterations MYB, LEF1, CDK20A, CDK20B, and NOTCH1 common to TALL were rare in T/M MPAL and ETP-ALL. Conversely, WT1 alterations were common in T/M MPAL and ETP-ALL, but uncommon in T-ALL. Gene expression profiling of T/M MPAL and ETP-ALL revealed similar expression patterns. The authors concluded that the extensive overlap of genetic alterations in T/M MPAL and ETP-ALL suggests a common progenitor cell of origin.

The co-expression of surface antigens associated with both myeloid and lymphoid lineages, as well as an enrichment in stem cell signatures in some cases of MPAL, raises the question of the cell of origin for MPAL. The authors examined the mutational burden of highly enriched hematopoietic stem and progenitor cell compartments in primary samples from patients with MPAL. In the cases examined, the authors consistently demonstrated a uniform distribution of case-specific somatic mutations between the malignant myeloid and lymphoid compartments of the leukemia. These findings are consistent with a model in which distinct combinations of genetic drivers target the primitive hematopoietic stem and progenitor compartments, giving rise to the clinical entities of MPAL, T/M MPAL, and B/M MPAL.

The data presented in this article support the need for both immunophenotype and genomic classification of MPAL. Second, the pediatric data must be viewed along with the genomic analyses in adult patients with MPAL given the recognition that age influences the genomic landscape of AML and ALL. Though limited, the genomic analysis of adult MPAL revealed mutations in genes associated with clonal hematopoesis (DNMT3A, IDH2), and these mutations are rare or absent in the pediatric cohort. Conversely, the ZNF384 rearrangements identified in the pediatric cohort were not identified in the adult studies. The genomic analysis also supports including patients with MPAL and specific genetic features in clinical trials, and offers background information for the design of such clinical trials using targeted agents. MPAL, though rare compared to other acute leukemia phenotypes, presents diagnostic and therapeutic challenges that necessitate better treatment protocols to secure optimal outcomes.

The potential role of thromboprophylaxis in ambulatory patients with cancer has long been an area of active investigation. In 2018, a meta-analysis of 28 randomized controlled trials concluded that low-molecular-weight heparin (LMWH) thromboprophylaxis resulted in a modest reduction in the incidence of symptomatic venous thromboembolism (VTE), though it was associated with a non insignificant increased risk of major bleeding. Despite this potential advantage, the use of thromboprophylaxis has not been widely adopted for multiple reasons, including the small increment of benefit, the burden and high cost of LMWH injections, and concerns for bleeding risk.

In the New England Journal of Medicine on December 4, 2018, the AVERT (Apixaban for the Prevention of Venous Thromboembolism in High-Risk Ambulatory Cancer Patients) investigators published the results of a novel approach to thromboprophylaxis in ambulatory patients with cancer. First, instead of LMWH, a reduced-dose direct oral anticoagulant, apixaban (2.5 mg twice daily) was used. Second, patients were selected using the Khorana score, a validated tool to identify patients at highest risk for VTE. Study participation required a Khorana score of 2 or higher, correlating with an estimated risk of symptomatic VTE at 19.6 percent for a score of 2, and 19.7 percent for a score of 3 or higher during the first six months of chemotherapy. Individuals with myeloproliferative neoplasms or acute leukemias were excluded. Approximately one quarter of the patients carried a diagnosis of lymphoma or multiple myeloma. A total of 574 patients were randomly assigned to receive thromboprophylaxis with apixaban or placebo, starting within 24 hours of initiation of chemotherapy and continuing for 180 days. A high-VTE-risk malignancy, as defined by Khorana score (e.g., pancreatic, gastric, or brain tumor), was present in 25.4 percent of patients; an intermediate–VTE-risk malignancy (e.g., bladder, lung, testicular, gynecologic, renal cancer, lymphoma, or multiple myeloma) was present in at least 22.1 percent of patients. The primary endpoint was objectively documented major VTE (proximal deep vein thrombosis (DVT) or pulmonary embolism (PE), either symptomatic or asymptomatic/ incidentally discovered). The main safety outcome was major bleeding.

There was a significantly lower rate of VTE in the apixaban group (4.2%) compared to the placebo group (10.2%) (HR 0.41; 95% CI 0.26-0.65; p<0.001), with a number of 17 needed to treat. The rate of DVT was 2.4 percent in the apixaban group and 4.4 percent in the placebo group, and the rate of PE was 1.7 percent and 5.8 percent, respectively.

The risk of major bleeding was higher in the apixaban group, occurring in 3.8 percent of patients compared to 1.8 percent in the placebo group (HR: 2.00; 95% CI: 1.01-3.95; p=0.048), with a number of 59 needed to harm. The rates of severe (category 3 or 4) major bleeding and clinically relevant nonmajor bleeding were similar in both groups. There was no significant difference in bleeding between the two groups (12.2% in the apixaban group, 9.8% in the placebo group; HR: 1.29; 95% CI: 0.98-1.71).

The AVERT trial appropriately concluded that in ambulatory patients with cancer and an increased VTE risk, thromboprophylaxis with apixaban 2.5 mg twice daily initiated at the time of chemotherapy significantly decreases the rate of VTE, with an associated comparatively smaller increase in risk of major bleeding.

As providers question whether and how to incorporate thromboprophylaxis into their practice, it could be helpful to consider the patient population included in the AVERT trial. For assessment of study enrollment eligibility, the Khorana score was first used, followed by consideration of the AVERT trial exclusion criteria. Below is a template for decision making regarding which patient to treat with apixaban 2.5 mg twice daily for VTE prophylaxis.

If a patient was eligible for the study by Khorana score, the next step required evaluation for AVERT exclusion criteria. Patients were excluded if they had “any condition that put them at an increased risk for bleeding.” This is an arguably subjective designation, and further details on what conditions were included in this category were not reported. Patients with a glomerular filtration rate (GFR) of less than 30 mL/min were excluded, and four patients (2.9%) in this study had a GFR of 30 to 50 mL/min. Notably, antplatelet therapy did not exclude patients from consideration — 22.8 percent of patients in the trial were receiving concomitant antplatelet agents.

How does this study influence our clinical management of ambulatory patients with cancer? For clinical purposes, it makes sense to follow the AVERT algorithm (Figure) as a template for potential treatment candidates or the development of designated anticoagulation clinics (as previously reported by Dr. Steven Ades and colleagues). The financial impact of apixaban must also be considered.

In conclusion, the AVERT data support a change in our approach to thromboprophylaxis in ambulatory patients with cancer, as the trial indicates that apixaban 2.5 mg twice daily is effective and relatively safe. Three major VTE events are prevented at the cost of one major bleed, the majority of which are not clinical emergent bleeds. An additional study of thromboprophylaxis with rivaroxaban is ongoing and is expected to shed further light on best management of ambulatory cancer patients at risk for VTE. The feasibility of incorporating patient selection, monitoring, and cost into clinical practice is an important consideration that requires further investigation.

Sickle cell disease (SCD) was first reported in the United States in 1910; however, the condition has been present in Africa for more than 5,000 years. An estimated 100,000 Americans struggle with SCD, which causes recurrent unpredictable episodes of acute debilitating pain, chronic organ damage, poor quality of life, and a two- to three-decade shorter life expectancy compared to unaffected individuals. Globally, SCD is much more prevalent, with more than a quarter of a million births annually in sub-Saharan Africa alone. Among the Igbo tribe in Nigeria (the most populous country in Africa), the term ogbanje, meaning “the child that comes and goes away,” or simply “the child who dies young,”1,2 the high death rate among children ascribed as ogbanje was reported by Dr. Esther Nzewi to correlate strongly with symptoms and a hematologic profile consistent with a diagnosis of SCD among 70 of 100 children studied.2

Decades of work in the United States have allowed some progress to be made in this disease, with advances to reduce the incidence of high infant and childhood mortality. But there is a dearth of interventions successfully implemented in African countries where SCD is more prevalent and extremely lethal in children. Hydroxyurea therapy has been incorporated into the standard of care for children and adults with SCD in the United States since the U.S. Food and Drug Administration (FDA) approval in 1998.3 The National Heart, Lung, and Blood Institute’s evidence-based report published in 2014 recommended offering hydroxyurea treatment to persons nine months and older with sickle cell anemia to ameliorate recurrent pain crises and acute chest syndrome and to improve anemia.4

Until recently, there have been very few studies of hydroxyurea use for SCD in sub-Saharan Africa, where the impact of this drug could potentially be greatest. The high cost of hydroxyurea in resource-poor countries creates challenges and there are also quality-assurance concerns with local manufacturing of hydroxyurea.5 Most families cannot afford the frequent blood monitoring required to achieve the maximum tolerated dose (MTD) recommended when using hydroxyurea in the United States. It is unknown whether hydroxyurea use for SCD in sub-Saharan Africa is associated with fewer deaths compared to the population with untreated sickle cell anemia, or whether this drug will cause more severe cytopenias. Lastly, conducting rigorous clinical trials is uniquely difficult in resource-poor countries and requires careful planning as well as robust stakeholder engagement to determine the most pragmatic study design that is both feasible and cost-effective.

In 2018, Dr. Leon Tolisano and colleagues published results of a large prospective phase III study titled Realizing Effectiveness Across Continents with Hydroxyurea (REACH) to demonstrate the safety and efficacy of hydroxyurea use among children in four sub-Saharan African countries including Angola, Democratic Republic of Congo, Kenya, and Uganda. This study was birthed from a partnership between U.S. Canadian, and sub-Saharan African investigators convened under the umbrella of the Global Sickle Cell Disease Network (GSCDN; http://wwwglobalsicklecelldisease.org). The REACH study investigated the safety and feasibility of using open-label hydroxyurea in children with SCD aged one to ten years in sub-Saharan Africa, across four clinical sites with a target of 400 enrolled subjects. Primary and secondary outcomes were screened during the 60-week laboratory data and clinical history. Oral hydroxyurea was then initiated at a dose of 15 to 20 mg/kg/d for the first six months before any dose escalation was attempted. The dose of hydroxyurea was escalated every two months thereafter if the absolute neutrophil count was greater than 4,000/mm³, hemoglobin was more than 6.5 g/dL, absolute reticulocyte count was higher than 150 x 10⁶, and platelet count was lower than 100 x 10⁶. Subjects were seen every month to assess for safety and efficacy for the first year and every two months afterward.

It is unusual in a clinical trial to incorporate and monitor standard-of-care guidelines for disease management; however, the REACH study provided an umbrella protocol guidance to address the a priori concern about the potential impact of co-existing management, nutritional deficiencies, and infections on the response to hydroxyurea. During the screening period, the protocol called for vaccination against measles and PCV13 (if not completed), PCV23 (if older than 2 years), nutritional supplementation based on dietary and anthropometry parameters, vitamin A supplementation with 200,000 IU orally (if younger than 5 years and not documented within the past 6 months), folate and iron supplementation, and malaria prophylaxis per local standards. Treatment for helminth infection with albendazole or mebendazole was required at study entry and repeated every six months, while vitamin A supplementation was repeated annually until completion of study.

A total of 606 subjects completed screening and initiated study treatment, and 90 percent of subjects documented no missed medical appointments. No subject was found to be at risk of adverse events resulting from SCD-related events (114.5 vs. 5.30 events per 100 patient-years; incidence rate, 0.47; 95% CI, 0.38-0.57) with reduction in both acute pain and acute chest syndrome rates. Surprisingly, the rates of infection also declined, including rates of nonmalarial infections (4.18 vs. 10.0 events per 100 patient-years; incidence rate ratio, 0.82; 95% CI, 0.53-0.72) and severe (grade 3 or higher) infections (28.9 vs. 8.60 events per 100 patient-years; incidence rate, 0.28; 95% CI, 0.19-0.42). This study also noted significantly reduced infections in male subjects (46.9 vs. 22.9 events per 100 patient-years; incidence rate ratio, 0.49; 95% CI, 0.29-0.81) and blood transfusion (40.3 vs. 14.2 events per 100 patient-years; incidence rate ratio, 0.39; 95% CI, 0.29-0.47), and death (3.6 vs. 1.1 events per 100 patient-years; incidence rate ratio, 0.30; 95% CI, 0.10-0.88).

The REACH study began enrollment in June 2014 and successfully enrolled 635 subjects in 30 months. Nearly 95 percent of subjects were retained on study for more than three years despite having to comply with monthly study visits for a year and bimonthly study visits thereafter.6 This is remarkably impressive and demonstrates the feasibility of conducting large clinical trials in SCD in resource-poor countries. It also implies that study participants and their families perceived value in their study visits, whether for access to hydroxyurea alone or access to the supportive care associated with being on the study. Hydroxyurea use led to a 50 percent reduction in malaria infection and consequently a reduction in transfusion rates. These findings are noteworthy because malaria infections have a high lethality rate among infants and children in sub-Saharan Africa, where transfusion safety is a persistent challenge.

It is not clear why there was a dramatic reduction in the rates of malarial and nonmalarial infections or if it had anything to do with hydroxyurea use specifically. The benefits of being a part of a clinical trial and receiving what should be standard of care (malaria prophylaxis, vitamin supplementation, etc.) could very well be responsible for this detected effect. Overall, the REACH study lays to rest several of the initial concerns with dosing hydroxyurea to MTD in countries where infections and malnutrition are high infant and childhood mortality. But there is a dearth of interventions successfully implemented in African countries where SCD is more prevalent and extremely lethal in children.

Dr. Daize Ennish and colleagues report a comprehensive genetic evaluation of a cohort of 157 germinal center B-cell (GCB)–derived DLBCL tumors, tumors (27%)1,2,3 including 22 (88%) of the 25 DLH tumors.4 It only missed three of the DLH in this cohort but included an additional 20 lymphomas that did not have double-hit cytogenetics. Despite this, the gene signature was associated with inferior treatment outcomes with R-CHOP, including shorter time to progression, decreased disease-specific survival, and decreased overall survival with the DHITsig-negative cohort. This inferior prognosis held for the non-DHL patients as well. The DHITsig remained significant in multivariable analyses and was not associated with other poor prognostic factors such as the International Prognostic Index or tumor volume. The genetic signature was validated in an independent cohort of GCB DLBCL. The signature was enriched for the upregulation of genes associated with the intermediate and dark, rather than light, zones of the germinal center, as well as for MYC and ETP targets, genes associated with cell proliferation, and MTO1C signaling. Additionally, these tumors had reduced expression of inflammatory and/or immune signatures, including CD4+ T-cell infiltrates, and loss of surface major histocompatibility complex molecules. Mutations in genes in general lymphoma such as CREBBP, EZH2, and KMT2D, as well as in TCF11 and DDX3X were more frequent in the DHITsig-positive group. Importantly, because RNAseq is not readily available as a clinical test for patients with newly diagnosed DLBCL, this group developed a clinically applicable NanoString-based assay using a 10-gene module to identify these patients in real time in a nonresearch setting. Using this test on a cohort of 347 patients, less than 5 percent of tumors were misclassified, and only approximately 10 percent of tumors were indeterminate. Most significantly, the prognostic significance of the DHITsig was indeed maintained with the DHITsig-positive and DHITsig-indeterminate tumors having significantly inferior outcomes.

This study signified the first investigation into the genetic and molecular mechanisms of which had double-hit lymphomas with the inferior outcomes seen in DHL. It defines a genetic signature that identifies not only 88 percent of DHL but an additional population of high-risk non-DHL patients that constitute 10 to 15 percent of GCB DLBCL. This work identifies new targets in these disease pathways and thus new opportunities for healthcare, including histone deacetylase inhibitors and drugs that target oxidative phosphorylation and the proteasome. Finally, the findings of this study will not remain of academic interest as they are accompanied by the development and validation of a clinically available test that can be used in a real-world setting.

Defining the Poor Prognosis of Double-Hit Lymphomas: Implications for Diagnosis and Therapy

A New Standard Emerges: Rational Use of Venetoclax to Inhibit BCL-2 Allows Treatment of AML in Older Patients


The time of diagnosis of their acute myeloid leukemia (AML), approximately 57 percent of patients are older than 65, with 33 percent older than 75 years of age. The SEER data demonstrates this trend to treatment given other comorbidities in these patients. Additionally, AML in older patients often responds poorly to standard induction regimens owing to a presumed lifetime of acquired genetic insults enhancing resistance properties in their leukemic stem cells (LSCs). Given historically poor clinical results in this context, novel therapies are much needed.

The hypomethylating agents (HMA) decitabine (DAC) and azacitidine (AZA) have long been a mainstay of myeloid therapies. Recently, the B-cell lymphoma 2 (BCL-2) protein was shown to play an important role in the survival of leukemia blasts as a key regulator of cell death in AML. Venetoclax, a potent, selective oral inhibitor of BCL-2, has previously demonstrated single-agent clinical activity in refractory AML.

Dr. Courtney D. DiNardo and colleagues have recently published results of a phase Ib dose-escalation and expansion study with the previously mentioned drugs for eligible patients 65 years of age or older with treatment-naïve AML. The study was initiated to conduct an intensive chemotherapy phase by age or comorbidities. Oral venetoclax was administrated daily as part of the dose escalation in combination with HMAs, dosed in the standard fashion.

Among all 145 treated patients, the median age was 74 years (range, 65-86), with poor-risk cytogenetics in 49 percent of patients and white blood counts (WBCs) 25 x 10^9/L or higher. Common adverse events were mostly gastro-intestinal, such as diarrhea, constipation, febrile neutropenia, fatigue, hypokalemia, decreased appetite, and decreased WBC. No tumor lysis syndrome was observed. Dose delays for neutropenia were required. With a median time on study of 8.9 months, 67 percent of patients (all doses) achieved complete remission (CR) or CR with incomplete count recovery. Thus, the combined response rate published was 73 percent for the combination. Patients with poor-risk cytogenetics and age 70 years or older had responses of 60 percent and 65 percent, respectively. The median duration of response was 11.3 months, and median overall survival was 175 months in all patients, but this metric has not been reached for the 400 mg venetoclax arm. These results are consistent with secondary AML (both 65% and 70%), and there were reasonable responses in patients with unfavorable molecular genetics such as mutations in TP53 or FLT3/ITD.

Similarly, Dr. Daniel A. Pollyea and colleagues recently provided rational data from the bench to explain these clinical results. Their group looked at an LSC-directed mechanism of Aza plus venetoclax in pre- and post-treatment samples from 33 patients who were treatment analogous to the aforementioned study by Dr. DiNardo and colleagues. These results were later compared with data from historical patients who received intensive induction. The authors were able to demonstrate deep and durable clinical remissions correlated with in vitro measurements of blast clearance. Through mass cytometry phenotypes, the methodically defined AML blast cell population was rapidly reduced, and specifically the LSC population. The authors found that a predictor of progression to MM.

Based on this study, overproduction of IL-17 seems to be the early event in disease progression, and given that anti–IL-17A and anti–IL-17B antibodies have been used to treat immune-related disease with relative success, it might be worth the effort to study whether targeting the IL-17–eosinophil immune axis could be another therapeutic intervention for patients with high-risk AML in an effort to prevent disease progression that can lead to irreversible end-organ damage and potential death.

The results of this study, overproduction of IL-17 seems to be the early event in the development of plasma cell growth. IL-17 was shown to promote tumor growth via the IL-6-STAT3 signaling pathway, which is critical for plasma cell growth. Taken together, these findings indicate a potential role for gut microbiota, Th17 cells, and IL-17 in regulating MM disease progression.

The Microbiome: A New Variable in Multiple Myeloma Disease Progression


Currently, due to MM treatment toxicity and a lack of accurate disease progression biomarkers, the standard of care for patients with SMM is observation until occurrence of symptomatic disease. However, during the past couple of years we have been testing therapeutic interventions for patients with high-risk SMM in an effort to prevent disease progression that can lead to irreversible end-organ damage and potential death.

Based on this study, overproduction of IL-17 seems to be an early event in disease progression, and given that anti–IL-17A and anti–IL-17B antibodies have been used to treat immune-related disease with relative success, it might be worth the effort to study whether targeting the IL-17–eosinophil immune axis could be another therapeutic intervention for patients with SMM at high risk for disease progression.
Beating AML: Know Your Enemy


In his ancient military treatise, The Art of War, Sun Tzu teaches the fundamental importance of a deep and detailed understanding of the enemy and the self in order to guarantee success on the battlefield. Despite the many advances in analytical genomics and a rapidly growing pharmacologic armamentarium, acute myeloid leukemia (AML) remains the archetypal enemy of patients and hematologists. Linking this knowledge of the enemy with our own strategies to treat leukemias remains a key and unmet need.

AML is a devastating blood cancer that leads to the death of more than 10,000 patients per year in the United States, and many more internationally. AML is genetically and phenotypically diverse, and this genetic heterogeneity has a major effect on survival after chemotherapy treatment. Molecularly targeted therapies have revolutionized the treatment of blood cancers; for example, the routine use of ABL kinase inhibitors in chronic myeloid leukemia, or ATRA plus arsenic in acute promyelocytic leukemia, both lead to long-term survival in more than 90 percent of patients. These initial spectacular successes have overshadowed the modest benefits from newer targeted treatments; however, it follows that specific targeting of oncogenic driver lesions may improve survival across many genetic subtypes of AML. The Beat AML trial, a large collaborative effort spearheaded by the Leukemia & Lymphoma Society, seeks to test this hypothesis in a prospective clinical trial designed to empower clinicians and patients by linking real-time genetic information with molecularly targeted therapeutic options.

In the first published results from the Beat AML Master Trial, Dr. Jeffrey W. Tyner and colleagues took an ambitious approach to integrate clinical, cytogenetic, molecular genetics, and transcriptional analysis, together with in vitro testing of primary samples, examining drug sensitivity against 122 different compounds. Both genetic factors and transcriptional signatures were associated with drug sensitivity. Genetic subgroups, including TP53 or ASXL1 mutations, were associated with widespread resistance in the drug screen, whereas other lesions (e.g., NPM1 mutations) showed resistance to many drugs but demonstrated sensitivity to MAPK pathway inhibition.

A major challenge in treating AML has been understanding the complex interactions between co-occurring genetic factors in the disease. Dr. Tyner and colleagues examined patterns of genetic cooperativity or mutual exclusivity and validated these in an independent patient cohort. For example, NPM1c mutation is one of the most frequent genetic alterations in AML, but was not found in AML/RARS or CBFR-MYH11 AML. In contrast, there was a strong positive association of NPM1c mutation with DNMT3A mutations. Combining these data with the in vitro drug sensitivity screen, the authors identified antileukemic activity of the tyrosine kinase inhibitors brutinib and entospletin in NPM1c-mutant or FLT3/ITD AML. However, this increased sensitivity was not seen in AML with FLT3ITD and concurrent DNMT3A mutation or sole DNMT3A mutations. The authors hypothesized that this may result from action against spleen-associated tyrosine kinase (SFK), though this was not specifically demonstrated.

To understand the mechanism of individual drug responses (Figure), the authors were able to generate unique gene expression profiles from primary AML samples with the highest 20 percent versus lowest 20 percent of responding samples for each drug. This was successful in 78 of the 112 drugs tested (FDR <0.05). Finally, the authors performed integrated, multivariate modeling to extend these findings beyond individual mutational or gene expression changes. Using this approach, they were able to identify co-occurrences of genetic mutations and gene expression clusters that predicted response. It will be fascinating to see whether these biological insights can be translated into meaningful patient responses on the therapeutic arm of the clinical trial.

Dr. Tyner and colleagues provide functional annotation of specific genetic AML subtypes using in vitro drug sensitivity screening and a systems approach to integrate cytogenetic, molecular, and gene expression data, mapping a path to clinical translation that will be tested in other aspects of the Beat AML trial. This article builds on the seminal work of Dr. Eli Papaeconomou and colleagues, who had previously used clinical trial data to correlate complex genetic factors with clinical response rates and survival after standard chemotherapy. These two major cohorts have some important differences; for example, the Beat AML cohort comprised an older group of patients (median age, 61 vs. 50 years) with fewer novel mutations. Importantly, the authors provide powerful online tools to interrogate clinical and genetic features in a portal that is accessible for clinical and research hematologists. Through this provision of publicly available, comprehensively annotated datasets, these results contribute to a global network of big data that can be used for follow-up projects that enables the testing or validation of translational hypotheses and new prognostic information. This work reinforces the finding that prognosis in AML is defined by tumor-specific factors, and is predominantly specified by responses to treatment. Effective algorithms that enable careful selection of the most appropriate and effective therapies are likely to be of utmost importance to improve survival for patients with this devastating blood cancer.

Note: ASH has partnered with the Leukemia & Lymphoma Society to help spread the word about the pivotal Beat AML trial.


The Hematologist: ASH NEWS AND REPORTS

The Cellular Pathway of Leukemic Transformation in MDS: It’s the Stem Cells, Stupid!


Myelodysplastic syndromes (MDS) are malignant hematologic diseases characterized by defective myeloid differentiation and high risk of transformation to secondary acute myeloid leukemia (sAML), which is associated with dismal clinical outcomes. MDS is propagated by rare and distinct MDS stem cells that accumulate somatic mutations. Previous bulk sequencing studies have demonstrated that acquisition of additional genetic and cytogenetic abnormalities correlates with progression of MDS to sAML, but the specific subset of cells in which this clonal evolution occurs has not been identified. Characterizing the cell-of-origin underlying transformation to sAML is essential to understanding the molecular events responsible for leukemic transformation in chronic myeloid malignancies, which will pave the way for early detection and interventions to prevent later disease progression.

Combining high-resolution targeted deep-sequencing of fractionated bone marrow populations and single-cell sequencing, Dr. Jiahao Chen and colleagues characterized the cellular architecture of clonal evolution in seven patients with MDS who progressed to sAML. Previous studies had suggested that sAML evolves from an ancestral MDS subclone that acquired further genetic mutations mostly in a linear and hierarchical fashion (Walter et al., 2012; Makushima et al., 2017). However, results from Dr. Chen and colleagues suggest that the evolutionary landscape of transformation might be more complex than previously thought.

Targeted sequencing of stem cells and blasts from longitudinal samples revealed that at both the MDS and sAML stages, stem cells were more genetically diverse than blast counterparts in the same patient. Consequently, only a subset of the genetic subclones present in stem cells could be identified in MDS or sAML blast cells analyzed at the bulk level. Subsequent targeted single-cell sequencing of the same populations confirmed that dominant clones identified in MDS blasts and sAML blasts frequently differed within the same patient, but all genetic subclones could be traced back to the stem cell compartment. These results support that genetically distinct subpopulations of stem cells within an individual patient give rise to MDS versus sAML blasts, leading the authors to propose a model of parallel rather than stepwise evolution in the progression to sAML.

Although further functional studies are now needed to elucidate the molecular and functional mechanisms of this process, the model proposed by Dr. Chen and colleagues substantially revises our current understanding of pathways to leukemic transformation in chronic myeloid malignancies. Furthermore, the key finding that genetic heterogeneity can differ markedly in stem cells versus bulk tumor populations has implications more broadly for precision oncology approaches, which typically involve analysis of total tumor populations. This study nicely demonstrated that genetic analysis of fractionated cell populations, including stem cells, can provide additional information that might more accurately predict disease course. Clearly, the challenge is now to analyze larger MDS patient cohorts, including stem cells, to provide additional information that might more precisely how genetic heterogeneity of stem cells correlates with risk of disease transformation.

Dr. Chen and colleagues identify previously unrecognized pre-leukemic stem cell heterogeneity in MDS prior to the development of sAML, which underlies disease transformation. Rather than stepwise linear evolution from an ancestral MDS subclone that acquired further genetic mutations mostly in a linear and hierarchical fashion, these results support that genetically distinct subpopulations of stem cells give rise to MDS versus sAML blasts, leading the authors to propose a model of parallel rather than stepwise evolution in the progression to sAML.

ALBA RODRIGUEZ-MEIRA, DPHE, AND ADAM J. MEAD, MD, PhD
Dr. Rodriguez-Meira and Dr. Mead indicated no relevant conflicts of interest.

STEVEN W. LANE, MBBS, PhD, FRACP, FRCPath
Dr. Lane indicated no relevant conflicts of interest.
Although multiple myeloma (MM) has long been considered incurable, newer therapeutic agents have led to such dramatic improvements in overall survival (OS) that earlier surrogate endpoints are essential for realistic and relevant clinical trial design. Further, complete response (CR) rates have risen (as high as 80%) with current treatment strategies such that the achievement of CR may no longer be sufficiently sensitive for outcome prediction.

Measurable residual disease (MRD; also referred to as “minimal residual disease”) assessment has been used in various hematologic malignancies as both an early and an analytically sensitive evaluation of disease response to therapy. The utility of MRD measurements in the context of MM was highlighted in a meta-analysis by Dr. Nikhil C. Munshi and colleagues. This study showed a 20% to 30% percent reduction in risk of progression and mortality in patients who achieved MRD negativity by multiparametric flow cytometry (MFC) or allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) – based methods. Differences between the hazard ratios in part reflect alterations in sensitivity of different MRD tests (MFC typically at least 10−3, ASO-PCR typically at least 10−4). Additionally, there are differences in clinical detection rates, with MFC having more wide applicability than ASO-PCR. In theory, deep sequencing of clonotypic rearrangements by next-generation sequencing (NGS) can achieve greater analytical sensitivity in assessing MRD (10−4) and therefore may prove superior to these other methods in predicting outcomes in myeloma. Although data are limited, retrospective studies have compared the results of NGS with other MFC or ASO-PCR.2,3 These studies demonstrated the applicability of this approach to 90 to 91 percent of patients and the prognostic significance of MRD status by NGS in terms of progression-free survival (PFS) and OS after induction chemotherapy and after autologous stem-cell transplantation.

A study published recently by Dr. Aurore Perrot and colleagues addresses the significance of serial MRD assessment by NGS using data from the phase III Intergroupe Francophone du Myélome (IFM) 2009 clinical trial, which evaluated the role of transplantation in patients with newly diagnosed myeloma treated with lenalidomide, bortezomib, and dexamethasone. The baseline clonal immunoglobulin gene rearrangements were defined using bone marrow aspirate enriched for CD138-positive plasma cells collected at enrollment. Subsequent samples were examined for MRD status before and after maintenance in patients achieving a very good partial response or better. The authors demonstrated that similar percentages of patients achieved MRD negativity (defined as <10−4) regardless of the treatment and other known prognostic factors such as stage of disease at diagnosis or cytogenetic risk profile, although those with del(17p) were less likely to achieve this status within the high-risk cytogenetic category. Patients who achieved MRD negativity at either timepoint had an improved PFS and OS at four years (from start of maintenance) compared to patients who were MRD positive post-induction, the level of measurable disease correlated with outcomes (Figure 1). Overall, MRD negativity alone conferred approximately 80 percent relative risk reduction.

The serial assessment of the study allowed the researchers to identify a subset of patients who changed MRD status after 12 months of maintenance therapy. A total of 10 percent of patients (27 of 270 patients) became MRD negative after maintenance, while 5 percent (12 of 270) became MRD positive despite initially being MRD negative. Interestingly, both PFS and OS were similar for patients with the same MRD status at the end of maintenance, regardless of their status at the initiation of maintenance (Figure 2). Further studies are required to determine if increased therapy at the early identification of relapse will affect the OS.

Two issues with this approach are evident. First, serial measurements for close monitoring of patients necessitates increased frequency of bone marrow biopsies. Second, bone marrow involvement is notoriously patchy, favoring a more wholistic assessment of response. In theory, the assessment of MRD in circulating tumor DNA (ctDNA) would address both these issues. However, recent work by Dr. Céline Mazzotti and colleagues demonstrated that 69 percent of MM patients who are bone marrow MRD positive by NGS do not have detectable ctDNA (18 of 26 cases), with an overall concordance rate of the two samples of only 49 percent.4

In conclusion, Dr. Perrot and colleagues have demonstrated the effective stratification of outcomes based upon the level of MRD as measured by NGS detection of clonotypes, supporting the concept of “the deeper, the better.” Serial evaluation of MRD demonstrated that up to 10 percent of patients can change MRD status during maintenance chemotherapy and that outcomes are dictated by the final MRD status at the end of maintenance. Although the NGS methodology used here fulfills many of the characteristics for an ideal MRD test as defined by Myeloma Working Group 6,5 the authors are careful to assert that likely any methodology with sufficient analytical sensitivity would provide similar results, but, in a separate study, ctDNA seems to be insufficiently sensitive/representative in myeloma. Additional studies will be required to determine the most informative and cost-effective time points for monitoring and appropriate interventions for MRD positive patients.
Treatment of Renally Impaired Patients With Venous Thromboembolism: Awaiting the VERDICT

**STUDY TITLE:** Venous Thromboembolism in Renally Impaired Patients With Direct Oral Anticoagulants (VERDICT)

**CLINICALTRIALS.GOV IDENTIFIER:** NCT02664155

**SPONSOR:** Centre Hospitalier Universitaire de Saint Etienne

**PARTICIPATING CENTERS:** Multiple sites in France

**STUDY DESIGN:** Randomized, open-label, non-inferiority

**ACCRUAL GOAL:** 800 patients

**STUDY SYNOPSIS:** This is a Phase III, randomized, open-label study comparing reduced doses of apixaban and rivaroxaban with standard-of-care in adult patients with symptomatic proximal deep vein thrombosis (DVT) or pulmonary embolism (PE) and reduced renal function. The primary outcome measure is net clinical benefit (recurrent venous thromboembolism [VTE] and major bleeding) at three months. Key exclusion criteria include high risk of bleeding, CrCl less than 15 mL/min, need for dialysis, or requirement for concomitant use of strong CYP 3A4 inducers or inhibitors.

Participants randomly assigned to the experimental arm will receive either apixaban 10 mg twice daily (bid) for seven days followed by apixaban 2.5 mg bid for three months or rivaroxaban 15 mg bid for 21 days followed by rivaroxaban 15 mg once daily for three months.

Participants randomly assigned to the control arm will receive heparin or low-molecular-weight heparin for a minimum period of five days followed by a vitamin K antagonist (VKA) for three months.

**RATIONALE:** Direct oral anticoagulants (DOACs) have been approved for treatment of VTE in patients with moderate to severe renal insufficiency in many countries, despite limited clinical evidence.

**COMMENT:** This study has the potential to provide much-needed high-quality clinical data. Less than 20 percent of patients in large randomized clinical trials comparing these agents with VKA had CrCl 30-50 mL/min and none had CrCl less than 25 mL/min.

A meta-analysis by Dr. Nick van Es and colleagues, including more than 27,000 patients with VTE, showed that DOACs were noninferior to standard of care for recurrent VTE and major bleeding.

Rationale:

**ClinicalTrialsCorner**

Dr. Linkins indicated no relevant conflicts of interest.

**JAKing up Targeted Therapy for Ph-like Acute Lymphoblastic Leukemia**

**STUDY TITLE:** A Phase 2 Study of the JAK1/JAK2 Inhibitor Ruxolitinib with Chemotherapy in Children, Adolescents, and Young Adults with De Novo High-Risk Cytokine Receptor-Like Factor 2- and/or JAK Pathway-Mutant Acute Lymphoblastic Leukemia

**CLINICALTRIALS.GOV IDENTIFIER:** NCT02723994

**SPONSOR:** Incyte Corporation in collaboration with the Children’s Oncology Group (COG)

**PARTICIPATING CENTERS:** 108 COG sites

**ACCRUAL GOAL:** 180 patients

**STUDY DESIGN:** AALL1521 is a nonrandomized, two-part phase II clinical trial designed to study the safety and efficacy of combining the JAK1/JAK2 inhibitor ruxolitinib with post-induction chemotherapy for pediatric patients with Philadelphia chromosome-like (Ph-like) B-Cell acute lymphoblastic leukemia (B-ALL). This study is enrolling children, adolescents, and young adults ages one to 21 years with newly diagnosed National Cancer Institute (NCI) high-risk (HR) Ph-like B-ALL, as defined by the general and in combination with chemotherapy (Loh ML et al. Blood. 2017;129:572-581; Roberts KG et al. N Engl J Med. 2014;371:1165-1175).

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Peter Robert Galbraith, MD, FRCP (1931-2018)

Dr. Peter Robert Galbraith graduated from Queen’s University in Kingston, Canada, in 1956. He then trained with Dr. William Dameshek in Boston, where he developed a lifelong interest in hematologic stem cells. He returned to Queen’s University and joined what he called the “division of blood and guts” with gastroenterologists Drs. Lesley Valberg and Malcolm Brown. In 1968, he was the sole founding member of a formal division of hematology, but he soon recruited Drs. David Ginsburg and Joe Pater. The division’s clinical responsibilities were extraordinarily wide by today’s standards, encompassing malignant and nonmalignant hematologic, medical oncology, and pediatric hematologic and medical oncology separated, so by the time he retired from full-time practice in 1996, the division focused exclusively on adult hematology.

Peter’s first academic interests were in human stem cell biology. His laboratory grew colonies in semisolid media from normal volunteer bone marrow samples. He observed that different colonies developed at different times in the cultures, and from this, he formulated an early version of a stem cell hierarchy concept. Unfortunately, funding in the 1980s became unfavorable, and his laboratory closed. Peter then turned his attention to hematologic education and realized the power of interactive computer-based programs as a tool to supplement his senior residents. His “HemaTeam” program was used in the undergraduate curriculum, and Peter continued to distribute it free of charge to the incoming Queen’s University medical class for several years after his retirement. Peter was also interested in residency education. He founded and directed the adult hematology subspecialty training program, from which many highly successful hematologists graduated. He instituted numerous weekly educational rounds on the clinical service, all of which persist to this day. He realized the importance of palliative care and early in his career was instrumental in introducing a clinical program at Kingston General Hospital.

Peter was an enthusiast for hematology, for ideas, and for life in general. He loved hematology and was happy to discuss stem cells for hours on end. He had an unbroken attendance record at the ASH annual meeting, stretching for more than 40 years. He attended as many sessions as possible and was always fascinated by new ideas. The social side of the meeting was also important to him, and he was excellent company for dinner and a humorous raconteur.

Peter married Ruth in 1954. They met as medical students. She was the love of his life, and he was much saddened when she predeceased him in 2013. He was adored by his three children, Meredith, Chris, and Leslie; five grandchildren; and three great-grandchildren.

From the academic and clinical standpoint, Peter Galbraith’s main legacy is the Queen’s University Division of Hematology. He wore large shoes, and his footprint in the division is visible to this day. His palliative care contribution is memorialized as the Queen’s University “Peter R. Galbraith MD Award for Palliative Care Education.”

— John Matthews, MBBChB
Queen’s University, Kingston, Ontario, Canada

This article presents the outcomes for all isoform dehydrogenase 2 (IDH2)–mutant patients with relapsed or refractory AML treated with the targeted drug enasidenib in this first-in-human phase II study. It reports data on molecular clearance and molecular relationships to response or resistance.


The authors describe a novel strategy for mitigating chimeric antigen receptor (CAR) T cell–associated cytokine release syndrome and neurotoxicity.

FEBRUARY 21, 2019


Venous thrombosis has been known to be a harbinger of malignancy since the days of Trousseau. Dr. Babak B. Navi and colleagues report that venous and arterial thromboses and strokes are also more common in the five months preceding a cancer diagnosis.


In this month’s CME article, Dr. Sophie Jones and colleagues challenge the prevailing recommendation that asymptomatic central venous catheter–related thrombosis in pediatric intensive care unit patients requires anticoagulation. In a prospective study of uninjured asymptomatic clots, they demonstrate an extremely low rate of clot extension or chronic sequelae.


In a Blood Spotlight, Dr. Pierre Fenaux and colleagues discuss the role of luspatercept, an activator receptor 2 ligand–based therapy, in the treatment of anemia in low-risk myelodysplasia and patients with primary myelofibrosis.

IN MEMORIAM

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— John Matthews, MBBChB
Queen’s University, Kingston, Ontario, Canada
An Unusual Consult
STEPHAN MOLL, MD
Professor of Medicine, Division of Hematology/Oncology, University of North Carolina School of Medicine, Chapel Hill, NC

I love being a coagulationist. Given our specialty, we are consulted by professionals from every aspect of medical care, from ob-gyn to neurology, nephrology, and sports medicine, and even the quality improvement and legal departments. The work is varied; the clinical questions are fascinating, and I enjoy interacting with and learning from other specialties.

And what unusual consults we get.

In October 2018, I received a phone call from one of the veterinarians at the the Duke Lemur Center, explaining that an adult male lemur had a “lame leg” and that a blood clot was suspected, asking, “How best to treat?” For some background, the Duke Lemur Center houses the world’s largest population of lemurs — small primates native to Madagascar — outside their native habitat. This conservation and research center located in Durham, North Carolina, is an 85-acre sanctuary for these endangered animals.

Never before had I been consulted for a “lame leg,” much less in a lemur. While “lame leg” is not a term we use in human medicine, veterinarians use it to describe an abnormal gait or stance that is the result of a dysfunction in the animal’s locomotor system. In the lemur’s case, the dysfunction was a suspected blood clot.

Charlie is a 12-year-old lemur. In September 2018 he received intravenous sedation through a catheter placed into the lesser saphenous vein (LSV) of his right leg to undergo an esophagogastroduodenoscopy for evaluation of possible gastritis. It was noted that immediately upon waking up, he did not use his right leg. Diagnosis: “lame leg.” One of the first thoughts of the veterinarian was that the catheter led to a superficial thrombophlebitis of the LSV, and because of associated pain, Charlie was not using his leg. A quick ultrasound of the vein suggested LSV obstruction. Aspirin administered over the next 10 days did not improve the symptoms. This then led to the call from the lemur center given my special interest in thrombosis and anticoagulation, asking if anticoagulants should be used, and what the next steps should be.

A 30-minute telephone conversation provided the information needed to develop a further management plan. Charlie had no leg swelling and no palpable cord. I wondered whether a superficial thrombophlebitis triggered by the LSV catheter during the procedure could have extended into the deep venous system and caused a deep vein thrombosis (DVT), such that Charlie should now be treated with anticoagulants. Our consult service pharmacist immediately, and with excitement, started to look at dosing of direct anticoagulants in light-weight humans (i.e., newborns and children). Charlie weighs 8 lbs (3.6 kg).

However, we wanted a solid diagnosis and not just initiation of empiric anticoagulation. We discussed obtaining a formal venous Doppler ultrasound of the leg by an ultrasonographer to assess whether a DVT was present and whether the veterinarian’s initial suspicion for superficial thrombophlebitis could be confirmed. The study was done, and the results were negative. Charlie did not have a clot.

The consult to the coagulationist essentially ended here; however, as a generous thank-you for the phone consultation and help, the veterinarian invited our consult team to a tour of the Duke Lemur Center. What a treat on a beautiful North Carolina autumn day, with colorful leaves on display and a crispness in the air. Unfortunately it was too cold for the lemurs to be out in the trees as they are native to much warmer Madagascar. We therefore visited the duke lemur center.

I love being a coagulationist. And I hope that Charlie will get better.