Heparin-induced thrombocytopenia (HIT) is a prothrombotic adverse reaction to heparin that may result in limb- or life-threatening thrombembolism. Traditionally viewed as an inevitable and inexorable complication of treatment with heparin, the primary focus of investigation and management in HIT has been on diagnosis and treatment, and little attention has been given to its prevention. Recently, investigators at Sunnybrook Health Sciences Centre in Toronto sought to change that.

Capitalizing on the observation that low molecular weight heparin (LMWH) is associated with a five- to 10-fold lower risk of HIT than unfractionated heparin (UFH),1 they implemented the “Avoid-Heparin Initiative” at their institution in 2006 with the lofty goal of preventing HIT. The protocol included four elements: 1) replacement of most prophylactic and therapeutic intensity UFH with LMWH (UFH was retained for hemodialysis and intraoperative anticoagulation during cardiac surgery), 2) replacement of heparinized saline flushes with saline flushes, 3) modification of order sets to exclude UFH, and 4) removal of UFH from most nursing units. Outcomes were compared in the pre-intervention (2003-2005) and postimplementation (2007-2012) phases.

The avoid-heparin protocol was successful in replacing UFH with LMWH. Overall use of LMWH increased fourfold during the study period. The relative risk reductions (RRRs) in HIT-associated outcomes were dramatic. Compared with the pre-intervention phase, the avoid-heparin protocol was associated with a decreased incidence of suspected HIT (85.5 vs. 49.0 cases per 10,000 admissions; p<0.001; 41.7% RRR), adjudicated HIT (10.7 vs. 2.2 cases per 10,000 admissions; p<0.001; 79.0% RRR), and HIT complicated by thrombosis (6.4 vs. 0.4 cases per 10,000 admissions; p<0.001; 90.7% RRR). The average annual estimated cost (in 2007 Canadian dollars) of HIT-associated care fell 82.8 percent from $392,951 to $55,383 after implementation of the avoid-heparin initiative. Benefits were observed across patient populations. The incidence of HIT was reduced 77 percent in cardiovascular surgery patients, 77 percent in other surgery patients, 75 percent in cardiology patients, and 62 percent in medical patients.

In this elegant quality-improvement study, institution-wide replacement of UFH with LMWH effected dramatic reductions in the incidence of HIT and HIT-associated thrombosis. Several limitations of this study deserve mention. It was carried out in a single center. Only a minority of patients underwent testing with the serotonin release assay (considered the gold standard for diagnosis of HIT). The approximately eightfold greater price tag for LMWH compared with UFH was not accounted for in the cost analysis.2 Despite these limitations, the study provides valuable proof-of-principle that HIT is, indeed, a preventable disease.

Quality metrics and reimbursement are increasingly linked to the incidence of preventable nosocomial diseases. Interventions to forestall selected nosocomial illnesses such as deep vein thrombosis, ventilator-associated pneumonia, central venous catheter–associated bloodstream infections, and pressure ulcers are listed in the Table.3–5 The RRR of the avoid-heparin protocol compares favorably with these widely used interventions, spurring the question as to whether institutions should be doing more to prevent HIT.

The analogy between HIT and the other nosocomial diseases in the Table is imperfect. HIT is probably less common. Therefore any intervention to prevent HIT, no matter how effective, may result in lower reductions in absolute risk and a greater number needed to treat. Moreover, a wholesale switch from UFH to LMWH may be more costly than targeted, less-expensive interventions (e.g., aspiration of subglottic secretions in mechanically ventilated patients). Nevertheless, the message from the study by Dr. Kelly McGowan and colleagues is clear: Institutional adoption of an avoid-heparin protocol is feasible and reduces the incidence of HIT. It may be time for clinicians, administrators, policymakers, and payers to re-envision HIT, not as an unavoidable atroфизicogenic disorder, but as a preventable nosocomial disease.

Table. Relative Risk Reductions Associated with Selected Interventions to Prevent Nosocomial Diseases

<table>
<thead>
<tr>
<th>Nosocomial Disease</th>
<th>Intervention</th>
<th>Relative Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep vein thrombosis†</td>
<td>Prophylactic intensity LMWH</td>
<td>44%</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia‡</td>
<td>Aspiration of subglottic secretions</td>
<td>45%</td>
</tr>
<tr>
<td>Central venous catheter-associated bloodstream infection</td>
<td>Chlorhexidine bathing</td>
<td>55%</td>
</tr>
<tr>
<td>Pressure ulcers§</td>
<td>Alternative foam mattress</td>
<td>60%</td>
</tr>
<tr>
<td>Heparin-induced thrombocytopenia</td>
<td>Avoid heparin protocol</td>
<td>79%</td>
</tr>
</tbody>
</table>

ADAM CUKER, MD, MS
Dr. Cuker indicated no relevant conflicts of interest.

Open Borders Open Minds

The ASH Executive Committee Retreat, held each year in the spring, is a wonderful way for committee members and senior staff to work and bond together. It is always rejuvenating and never fails to generate new ways of bettering the mission of ASH. The retreat location is key to stimulating an environment of innovation, inspiration, free communication, and an open and collaborative mindset. As ASH President, one of my roles is to select the location for this event, and this year, the location I chose was Havana, Cuba, which turned out to be the perfect choice. Cuba is a close neighbor of the U.S., yet vastly different in multiple respects. I think that the experience of immersion into a non-U.S. society (something we typically do not have the chance to experience at these retreats) is part of what spurred many of us to be even more introspective and flexible than usual. Furthermore, the sheer cultural richness of Havana and its people added to the mosaic of personalities, augmented the retreat environment, made a distinct contribution to the dialogues in which we participated, and highlighted the extraordinary diversity among the retreat participants. We have so much to learn from one another, and indeed we did.

It cannot be overstated how much this unique setting allowed us to think about our work as hemato logsists in new ways. We were limited in our use of the internet and cell phones—a shock at first, but ultimately a gift. “Shutting down” from technology for several days allowed for fertile ground to communicate one-on-one even more effectively and intimately.

If you have followed the news over the past year and a half, you know that this trip would not have been possible for ASH without the improvement and evolution of diplomatic relations between the U.S. and Cuba. Until the retreat, for even the most widely traveled among us, Cuba represented, quite literally, an unfi nable destination. Many of us knew that it would be a place frozen in time in many ways, best symbolized perhaps by the fabulous pre-Cold War automobiles. However, the educational exchange with my counterpart at the Cuban Society of Hematology (CSH), Dr. Antonio Bencomo, and with numerous CSH members, allowed us to look into the future of our field, learning about novel treatment approaches, and identifying much more common ground with our Cuban colleagues than some might have anticipated.

We learned a great deal about the Cuban health-care system, which makes free care and treatment available to all. We talked about the use in Cuba of partial splenectomies for pediatric patients with sickle cell splenic sequestration crisis, and about their treatment inductions and consolidation methods for the management of acute leukemia. The latter conversation, among others, revealed many differences between our approaches and underscored that perhaps “the American way” may be neither the best nor the only. In the case of bone marrow transplantation, the ASH and CSH contingencies were excited by the many similarities we share. Moments like these further spotlighted the critical nature of learning from each other across borders. They make us look forward to engaging in more than just one-way talks and lectures, toward opening up more meaningful discussions and interchanges of ideas.

The very roots of the word retreat mean to pull away or to take a step back. And in fact, we were able to use this occasion to step back and reposition ourselves to get a better view of the big picture of hematologic care and what it means to ASH’s members and those whom we serve. ASH exists to help patients with blood diseases worldwide. This is why we help to educate hematologists on best practices, fund researchers, and advocate for better health-care policy. It is why we strive to help hematologists to better understand everything from clinical trials to the molecular basis of various diseases. Our experience in Cuba solidified that there is an incredible value to “bridging conversations,” in which we examine different approaches all across the globe. The reality is that we can do a lot to effect change by reanalizing the practices we accept as standard. It also became clear that we must do more to examine and understand the availability of drugs in different places around the world, and how that impacts care for all people. This is what it means to be “a global society,” and ASH is at the forefront of helping to make a difference internationally.

ASH programs such as the International Consortium on Acute Leukemia (www.hematology.org/Global206.aspx) exemplify how building collaborative relationships from nation to nation can make tremendous progress toward standardized practices around the world. And in the same way that we as hematologists are in a constant state of growth and place a high premium on lifelong education, hematology as a whole still has plenty of room to mature and expand. Havana and the Cuban hematologists we met illuminated the importance of looking beyond our own backyards, maintaining open minds, and doing everything we can to share our unique experiences with each other.

To learn more about ASH’s global programs and to become involved, visit www.hematology.org/Global.
Abstract Submission for the 2016 ASH Annual Meeting Now Open

Consider presenting your research at the 58th ASH Annual Meeting, the world’s premier hematology event. Abstract submission across 62 scientific and clinical categories, spanning the entire field of hematology, is now open. The submission deadline is August 4, 2016, at 11:59 p.m. Pacific Time. Visit www.hematology.org/Annual-Meeting/Abstracts/ for more information on attending and presenting at this year’s meeting in San Diego. Please also note that early-bird registration and housing (ASH members only) opens on July 20, 2016, at 11:00 a.m. Eastern Time.

ASH-SAP, Sixth Edition Now Available

The sixth edition of the ASH Self-Assessment Program (ASH-SAP) is now available for ordering. This educational resource will help hematologists and others working in hematology-related fields to stay up to date with the latest advances in the rapidly evolving disciplines of adult and pediatric hematology including benign and malignant disorders.

ASH Award for Leadership in Promoting Diversity

The 2016-2017 Honorific Awards Nomination and Review Cycle is now open. Nominations for the ASH Award for Leadership in Promoting Diversity will be accepted through August 1, 2016. This NEW award is intended to honor an individual who has demonstrated extraordinary commitment to diversity and inclusion in hematology. The scientific accomplishments of this individual are relevant in as much as they are related to diversity and inclusion. Nominees should have a recognized record of accomplishment that has a specifically identifiable focus on promoting inclusion and diversity in hematology. These contributions should be recognized broadly as contributing to hematology research, education, mentorship, clinical practice, administration, advocacy, or a combination of these categories. Nominees should be actively involved in the advancement of diversity and the inclusion of under-represented groups, such as women and racial/ethnic minority populations. The recipient need not be a member of such an under-represented group.

Visit www.hematology.org/Awards/Honorific/ to learn more about this new opportunity to recognize your peers.

Free CME Summit on Myelodysplastic Syndrome

There are many complexities associated with Myelodysplastic Syndrome (MDS) that a multispecialty team must address as a clinical-care unit. To address educational gaps associated with these complexities, the American Society for Clinical Pathology (ASCP), the American Society of Hematology (ASH), and the France Foundation have designed comprehensive MDS-directed educational summits that feature live events designed by world-class subject matter experts. For more information on these complimentary events and to register, visit www.hematology.org/MDS.

Register for the ASH Meeting on Hematologic Malignancies

The 2016 ASH Meeting on Hematologic Malignancies (MHM) will take place September 16-17 in Chicago. Top experts in hematologic malignancies will discuss the latest developments in clinical care through "How I Treat" sessions; presentations will showcase the speakers’ evidence-based treatment approaches, including standard of care, specialized disease complications, and novel agents. Peer-reviewed clinical research will also be presented. Learn more at www.hematology.org/Malignancies.
The Question
What is your diagnostic approach to monocytosis?

Case
A 73-year-old woman has had monocytosis for at least seven years. She has a history significant for rheumatoid arthritis and anemia of chronic disease. In 2010, her white blood cell count was 9.8 × 10^9/L with 59 percent neutrophils, 19 percent lymphocytes, and 21 percent monocytes (absolute monocyte count 2.1 × 10^9/L). For her blood count was 3.2 × 10^9/L, hemoglobin was 10.0 g/dL, mean corpuscular volume was 91.5 fL, and platelets were 162 × 10^9/L. The peripheral smear did not show immature monocytes. A bone marrow biopsy performed at that time was normocellular for age (40%).

Significant findings were limited to increased mature monocytes (12% by manual differential) and mild dyserythropoiesis (-10%). Flow cytometry showed no increase in blasts (0.3% CD34 positive events), polytypic B-cells, and phenotypically normal T-cells. A concurrent unstimulated karyotype was normal.

Six months later, the absolute monocyte count remained elevated at 1.3 × 10^9/L, and a repeat bone marrow biopsy with flow cytometry and cytogenetics reported similar results.

Our Response
Examining the Blood Smear
Peripheral smear review is essential in cases of sustained monocytosis because morphology is critical to correct classification and diagnostic testing recommendations. Morphology is required to assess maturity in monocytes and to distinguish between monocytes and promonocytes. This difference is crucial since promonocytes are blasts equivalents and should be included in the blast count.

Additionally, assessment for dysplasia is required, as this provides critical information. In the setting of normoblastosis, bone marrow stress, rheumatoid arthritis, and other autoimmune disorders, dyserythropoiesis in blood may be observed, so assessment of red blood cells is not as useful as neutrophil evaluation. If dysplasia is present, it should be noted and the blast-equivalent promonocytes, and to distinguishing them from mature monocytes, both reactive and dysplastic. As already mentioned, this distinction is not possible by flow cytometry. Cytotoxic staining may be useful since it improves the sensitivity over morphology alone for the detection of monocytic cells.

Based on World Health Organization (WHO) 2008 criteria, the diagnosis of CMML requires at least three months of monocytosis (1.0 × 10^9/L) with dysplasia in at least one myeloid lineage. When dysplasia is absent, the presence of an acquired cytogenetic or molecular clone is required. Other disease-defining translocations, notably BCR-ABL1 fusion, must not be present. In the setting of CMML, one must also be on the lookout for systemic mastocytosis, which may be seen concurrently. CMML is the myocard malignancy most frequently described in this setting. In the upcoming revision to the 4th edition of the WHO criteria, further subtypes of CMML with prognostic significance may be acknowledged. Based on a WBC count above or below 13 × 10^9/L, a proliferative and dysplastic subtype, respectively, can be assigned. Additionally, “CMML-0” will be introduced for cases in which the blast count is less than 2 percent in the peripheral blood and 5 percent in the bone marrow.

Cytogenetic abnormalities are seen in a majority of cases of CMML (approximately 30%). The detection of a clonal cytogenetic abnormality, with few exceptions, confirms a neoplastic process. In contrast, a positive molecular result does not confirm a neoplastic process, since mutations are detected in normal subjects. Mutations in confirmed cases of CMML are found in nearly all cases. Many somatic mutations have been described in CMML, although none are specific to the disease. Some of the most common mutations are TET2, ASXL1, SRSF2, and SETBP1. In some cases, SRSF2 is the most common mutation, and it is often seen in the setting of a normal karyotype. SETBP1 and ASXL1 are associated with reduced overall survival. RUNX1 has been associated with a worse prognosis. NPM1 mutations have been linked to a higher transformation to acute leukemia in a high percentage of cases.

Interestingly, recent literature has shown that approximately 10 percent of individuals older than 70 years harbor a mutation in peripheral blood, many of which are seen in CMML, including ASXL1 and TET2.

This finding shows that, in contrast to cytogenetic abnormalities, the detection of an isolated molecular abnormality in a case of monocytosis does not necessarily confirm a neoplastic diagnosis.

The incidence of transformation from CMML to AML is variable, ranging from 15 to 52 percent. Sequential karyotyping has prognostic value, in that approximately 25 percent of CMML patients will acquire cytogenetic abnormalities not present at diagnosis. Not surprisingly, the development of a complex karyotype is associated with progression to AML. Those with the addition of del(20q) tend to have stable disease.

Patient Follow-up
In this patient, the absolute monocyte count has fluctuated but has remained elevated since at least 2010, ranging from 0.9 to 10 × 10^9/L. Platelet counts have remained mildly decreased (102 × 10^9/L to 157 × 10^9/L), and anemia has never been present. In 2015, the absolute monocyte count was 3.2 × 10^9/L, which triggered a flow cytometry study on peripheral blood. This showed 62 percent monocytes with partial expression of CD56, but without additional immunophenotypic abnormality. A subsequent CBC several months later showed a stable monocyte count of 3.1 × 10^9/L.

Overall, the findings in this case are consistent with a reactive monocytosis. In rheumatoid arthritis, as in other autoimmune disease, monocytosis is seen in a significant minority of patients and is typically mild. The monocytosis has been stable, and significant dysplasia is not present in the peripheral blood or bone marrow. Repeat bone marrow biopsy with karyotype failed to reveal evidence of a neoplastic process. In this setting, pursuing molecular studies to detect a mutation is not clearly indicated and may even lead to an erroneous diagnosis. Given the relatively high prevalence of mutations of clonal hematopoiesis of indeterminate potential, the finding of one of these mutations would not be diagnostic of a myelodysplastic syndrome. As already mentioned, monocytosis would be of great value in making a diagnosis, and this could be potentially performed on peripheral blood.

Monocytosis is both a common and challenging finding. Accurate diagnosis of the many entities which present as monocytosis requires the use of history, morphology, and the judicious use of ancillary studies.

References
ASH in Cuba

(Cont. from page 1)

opportunity existed to visit Cuba to advance its global mission of hematology education, patient care, and research. I accompanied ASH’s Executive Committee and senior staff to the 10th Annual Executive Committee Spring Retreat, held this year in Havana.

One of the highlights of the retreat was an educational exchange with some 40 members of the Cuban Society of Hematology (CSH). The CSH consists of 294 members, including 154 hematologists who serve at 39 clinical facilities (25 adult and 14 pediatric hospitals) in all provinces of the island nation. The agenda was comprised of a translator-facilitated discussion of the American and Cuban approaches to the management of three hematologic diseases. Drs. Alexis Thompson and Sergio Machín García discussed sickle cell disease, leukaemia and acute promyelocytic leukaemia were delivered by Drs. Martí Tallman and Carlos Hernández-Padrón; and Drs. Alixon Loren and Alejandro González Otero gave updates on acute lymphoblastic leukemia. I had the opportunity to learn more about the practice of hematology in Cuba from the President of the CSH, Dr. Antonio Bencomo. I was particularly interested in hearing him paint a picture of how the deep long economic squeeze of the Cuban economy has impacted the availability of medicines commonly used in the U.S. as part of standard care approaches to malignant and nonmalignant hematologic disorders.

Dr. Bencomo reiterated that the Cuban health-care system guarantees all of its patients’ necessary medicines according to the precept of universal and free care. Expensive medications that constitute a second- or third-line therapy may be available through treatment protocols established through Cuba’s national system of health and medical specialties. In many cases, access to new drugs is difficult because of the limitations placed upon companies to restrict their sale to Cuba. The U.S. 1992 Cuban Democracy Act made it more difficult to purchase medications from U.S. companies or their foreign subsidiaries. The 1996 Congressional Helms-Burton Act stipulated that any non-U.S. companies (including pharmaceutical and biotechnology firms) were subject to lawsuits in U.S. courts if they engaged in trade with Cuba.1,2 Because the overwhelming majority of drugs are either produced in the U.S. or by European companies that have merged with U.S. firms, this decimated Cuba’s access to medicines, vaccines, medical devices, and diagnostic equipment. Although the U.S. has provided humanitarian donation of medicines and medical supplies, and authorizations for some medicines have been granted, complicated banking, licensing, and shipping policies frustrate the import of such lifesaving materials.

Cuban resourcefulness and self-reliance have overcome some of the external limitations imposed on Cuba to produce their own medicines. The Centro de Immunología Molecular (CIM), which opened in 1994, is Cuba’s premiere research, production, and biotech campus. CIM’s biotechnology focus is on normal and malignant cells, as well as the production of monoclonal antibodies and cancer vaccines. Their paradigm is to use treatments such as immunotherapy as a major strategy to treat cancer a chronic disease, with less of a focus on cure. It has 1,136 employees and houses laboratories and animal facilities. CIM is part of the CUBASIPHARMA holding group that has 21 products in the pipeline (six registered) and 48 patents, and exports products to 31 countries. There are 78 manufacturing facilities, including several in other countries (such as Japan and Brazil). In all, it has 27,785 workers, of whom 282 have PhDs. The Roswell Park Cancer Institute and Moffitt Cancer Center have existing drug development partnerships with CIM.

Dr. Bencomo pointed out that Cuban biotechnology also produces and commercializes erythropoietin (EPOCIM®) by CIMAB SA, and filgrastim (HeberHep®) by Heber Biotec SA. Arsenic (Arsenic®) is also produced domestically; it has been added to ATRA, which was incorporated by Cuba into APL therapy in 1991 (one of the first countries to do so). For patients with venous thromboembolism, low-molecular weight heparin and coumadin are available, with the latter also being produced by the Cuban pharmaceutical industry. The new oral anticoagulants are not widely available, but may be given to patients after failure of initial treatment. Dr. Bencomo provided some additional disease-specific examples of available therapies in Cuba:

- **Chronic myeloid leukaemia.** All patients are treated with imatinib (Gleevec® and generic). Resistant patients are given nilotinib; standard or regrafted populations of interferon-α are available (Heberon Allia®; PEG-Heberon) and produced by Cuban biotechnology (Heberbiotech SA).
- **Chronic lymphocytic leukaemia.** Patients younger than 60 years receive fludarabine, cyclophosphamide, and rituximab; cyclophosphamide, vincristine, and prednisone is administered to patients older than 60 years. Ibrutinib and ibrufilxizab are still not considered front-line therapy and could be made available after an unfavorable response to conventional therapy.
- **Myelodysplastic syndromes.** In addition to the aforementioned use of Cuban-manufactured erythropoietin and filgrastim, thalidomide is often the first choice for lower-risk MDS, including del(5q) MDS. Azacitidine is the first-line therapy for higher-risk MDS and a second-line option for subjects with lack of response or intolerance to thalidomide. After failure of these “conventional” agents, access to lenalidomide or decitabine is possible. For MDS and other diseases, there are 46 blood banks in the country that provide blood components from voluntary donors.

Flow cytometry, standard karyotyping, fluorescence in situ hybridization, and molecular analyses are all available for the diagnosis of hematologic malignancies. Patient samples are sent for central analysis at the Institute of Hematology and Immunology (IHI) in Havana. The IHI, a research institute created in the 1960s by the Ministry of Public Health, leads the national effort in scientific investigations of hematologic diseases (e.g., sickle cell anemia, hemophilia, leukaemias) and immunologic disorders. In addition to establishing quality assurance standards for transfusion medicine, histocompatibility testing, and related fields of immunohematology, IHI’s mission is to provide postgraduate training of physicians in hematology and training of health technicians to cover the nation’s needs in these subspecialty areas. The IHI intermediates well with Dr. Bencomo’s stated mission of the CSH — to ensure the scientific development of its members so that they can satisfy the needs of their patients. CSH, in conjunction with the IHI and their National Hematology Group (Grupo Nacional de Hematología) project labor needs in the areas of hematology, immunology, transfusion medicine, and regenerative medicine. He cited that CSH’s area of greatest interest is the use of advanced technology to improve diagnosis and to achieve a greater percentage of cures for patients with hematologic malignancies, including the use of unrelated donor and haploidentical hematopoietic cell transplantation.

Dr. Bencomo touched on the feasibility of conducting clinical trials in Cuba. He indicated that the country has a guiding Center of Clinical Trials (CENEC) which belongs to the Ministry of Public Health (MINSAP). It is responsible for the coordination and implementation of clinical trials for all medical specialties, including hematology, and ensuring compliance with international clinical trial standards. There is also a public registry of clinical trials that is accessed through the portal of Indeplt (http://registroclinicos.sld.cu/). Dr. Portorio Hernández and colleagues from the IHI have led Cuba’s clinical trial efforts in regenerative medicine. Since 2004, they have studied the effects of intramuscular or intra-arterial administration of autologous bone marrow mononuclear cells (BM-MNC) or peripheral blood MNC mobilized from the BM with filgrastim. The indications for treatment have included critical lower limb ischemia due to arterial insufficiency with criteria for amputation; lymphedema; orthopedics and trauma (bone cysts, complex bone fractures, aseptic necrosis of the hip and degenerative joint injuries); periodontitis; and paraplegia due to spinal cord injury. Dr. Hernández cited that in 73 percent of patients with critical lower limb ischemia and criteria of major amputation, this intervention was avoided; in patients with intermittent claudication, improvement was obtained in 85 percent of cases. Their group has also evaluated the role of platelets in regenerative medicine. By the end of 2014, 5,533 units of platelet components, primarily for orthopedic and “angiology” indications had been used for such trials. Other regenerative uses of platelets have included burns; skin ulcers; and in the form of eye drops for treatment of injuries of the cornea and dry eye due to low production of tears. In the decade following treatment of the first patient in 2004, the number of units supplied either with stem cells, platelets, or both combined, reached 13,045, making Cuba among one of the nations with the most widespread application of regenerative medicine. Randomized, controlled trials are needed to definitively establish the efficacy and safety of these regenerative medicine efforts.

The highly advanced training of Cuban doctors is widely acknowledged. Cuba has one of the highest ratios of doctors to residents in the world, and the country places a high priority on medical care, like it does for education. However, it is also well known that doctors’ pay, like that of everyone

Pictured (L-R): Dr. Jason Gotlib, Dr. Portorio Hernández, and Dr. Robert Negrin during the 2016 educational exchange in Havana.
Management of Venous Thromboembolism: An Update of the ACCP Guidelines

DAVID GARCIA, MD
Professor, Division of Hematology, University of Washington, Seattle, WA

MINI REVIEW

In early 2016, the latest version of the widely read evidence-based guidelines for the treatment of venous thromboembolism (VTE), sponsored by the American College of Chest Physicians (ACCP) was published in the journal Chest. In this Mini Review, I will highlight some of the clinical recommendations that are most relevant to hematologists.

As in previous iterations of these guidelines, the authors grade each recommendation depending on two factors: the lopsidedness of the risk-benefit tradeoff and the strength of the supporting evidence. The strongest possible recommendation is graded “1A,” where the “1” indicates that the risk-benefit tradeoffs are such that most patients and physicians would, in light of the evidence, choose to follow the recommendation, and the “A” indicates that the quality of evidence on which the recommendation is based is high (e.g., more than one randomized controlled trial showing a similar treatment effect). At the opposite extreme, a “2C” recommendation would correspond to an intervention for which different patients or physicians see the risk-benefit tradeoffs differently and for which the quality of the evidence is low (e.g., data from an observational, noncontrolled study).

1. “For VTE and no cancer, as long-term anticoagulant therapy, we suggest dabigatran (Grade 2B), rivaroxaban (Grade 2B), apixaban (Grade 2B), or edoxaban (Grade 2B) over Vitamin K Antagonist (VKA) therapy.”

This decision to suggest (albeit not strongly) that a direct oral anticoagulant (DOAC) be used preferentially over warfarin is important because many hematologists had been reluctant to choose this class of medications to treat deep vein thrombosis (DVT) or pulmonary embolism (PE). The authors of this guideline, citing numerous large randomized controlled trials that compared DOACs to warfarin in both atrial fibrillation and VTE, explain that their preference for DOACs is based on the evidence that DOACs are as effective as warfarin but cause less bleeding (especially intracranial hemorrhage). They mention the increased convenience (no anticoagulation monitoring and essentially no dietary interactions) afforded by this class of medications. It is noteworthy that the authors made this recommendation despite the fact that, at the time the guideline was written, no reversal agent for any of the Xa inhibitors was approved for use. The authors reinforced the need to incorporate a patient’s preferences into the final decision about treatment, and they may have chosen a strength of “2B” (rather than “1B”) partly to recognize the financial burden that DOACs can present for many patients.

2. “For VTE and cancer, we suggest LMWH [low molecular-weight heparin] over VKA (Grade 2B), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C), or edoxaban (Grade 2C).”

Although prescribing a DOAC to a patient with cancer-associated VTE would not be an “off-label use” in the United States, this recommendation reflects the lack of studies comparing DOACs to long-term LMWH, the current standard of care in this setting. At least one randomized controlled trial of a DOAC (edoxaban) versus LMWH (dalteparin) is underway.

3. “In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk (see text), we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B), and a (ii) high bleeding risk (see text), we recommend 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 1B).”

This recommendation, unchanged from the prior version of these guidelines, highlights the importance of determining whether a clot was provoked or unprovoked when determining duration of anticoagulant therapy. Although the authors are recommending that many VTE patients receive “extended” therapy without a stop date, the absence of the phrase “lifelong anticoagulation” is conspicuous, and the authors emphasize the need to periodically re-assess the risks and benefits of anticoagulation in all such patients. Some of the factors that have been independently associated with an increased risk of major bleeding on warfarin are listed in the Table. The authors suggest that for patients with unprovoked VTE who have none or one of these bleeding risk factors, the risk of ongoing anticoagulation will likely be outweighed by the benefit.

4. “For DVT, we suggest not using compression stockings routinely to prevent PTS [post-thrombotic syndrome].”

Prior iterations of these guidelines had suggested that compression stockings be used, based on observational studies that were subject to bias. The new recommendation against the use of these stockings reflects the negative result of a randomized trial in which compression stockings were compared to “sham” stockings.1

As in previous iterations of these guidelines, the authors grade each recommendation depending on two factors: the lopsidedness of the risk-benefit tradeoff and the strength of the supporting evidence.

Table. Factors Associated with an Increased Risk of Bleeding on Warfarin*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Older age</th>
<th>Antiplatelet therapy</th>
<th>Renal failure</th>
<th>Comorbidity and reduced functional capacity</th>
<th>Liver failure</th>
<th>Recent surgery</th>
<th>Thrombocytopenia</th>
<th>Frequent falls</th>
<th>Previous stroke</th>
<th>Alcohol abuse</th>
<th>Diabetes</th>
<th>Nonsteroidal anti-inflammatory drug</th>
<th>Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adapted from Kearon et al. It is unknown which of these factors will be associated with an increased risk of bleeding among patients treated with other anticoagulants (e.g., low molecular-weight heparin or direct oral anticoagulants).

In patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy (Grade 1B).”

This affirmation of a recommendation from the prior guidelines is based, for the most part, on the Pulmonary Embolism Thrombolysis trial, which randomly assigned 1,006 patients with PE and right ventricular dysfunction to tenecteplase and heparin, or to heparin alone (with placebo). Although thrombolytic therapy reduced the risk of hemodynamic collapse, it also increased the risk of major (including intracranial) bleeding. The authors of the present guideline concluded that this new evidence was consistent with what had been demonstrated in prior studies: for most PE patients without hypotension, thrombolytic therapy does not confer a net benefit over anticoagulation alone. In associated comments, the authors acknowledged that the PE patients without hypotension who have signs of significant cardiopulmonary impairment will be best managed in a setting where any deterioration can be detected rapidly. Indeed they suggest that a patient with low bleeding risk who deteriorates while on anticoagulant treatment should receive systemically administered thrombolytic therapy.


As in previous iterations of these guidelines, the authors grade each recommendation depending on two factors: the lopsidedness of the risk-benefit tradeoff and the strength of the supporting evidence.
ASH Committee on Practice Hits the Hill for Sickle Cell Disease and Access to Affordable Treatments

Following its May 23, 2016, meeting in Washington, DC, the ASH Committee on Practice visited more than 40 congressional offices on May 24 to advocate for issues related to sickle cell disease (SCD) and drug access. ASH advocates encouraged congressional offices to urge the Center for Medicare & Medicaid Innovation (CMMI) to develop a demonstration program focused on improving care for individuals with SCD. The group also asked members of Congress to support legislation (the Patient’s Access to Treatments Act, H.R. 1600; www.congress.gov/bill/114th-congress/house-bill/1600), that establishes patient cost-sharing limits for high-cost drugs in health plans that cover prescription drugs.

Congressional meetings are an important component of ASH’s advocacy efforts and provide an opportunity for members of Congress and their staffs to gain insight on issues of concern to hematologists and their patients. However, the Society needs its members’ help in bringing these important issues to the attention of the U.S. Congress and other governmental agencies.

ASH strongly encourages members to let the ASH Government Relations and Practice department know when you are in Washington, DC, and are available to meet with your congressional delegation. ASH staff can assist by arranging appointments so that your voice is heard in the halls of Congress. You can also participate in the Society’s advocacy efforts by visiting the ASH Advocacy Center and joining the ASH Grassroots Network. Contact ASH Legislative Advocacy Manager Tracy Roades at troades@hematology.org, or visit www.hematology.org/Advocacy for additional information.

ASH Comments on Plan to Change Payment for Physician-Administered Drugs

In May, ASH submitted detailed comments on the proposed Medicare Part B Drug Payment Model, which would change the formula for physician-administered drugs in many of the United States, reducing payments for expensive drugs, including cancer treatments, and allowing for the use of innovative drug payment models in certain geographic locations. The Medicare Part B demonstration model is proposed to change the payment formula for physician-administered drugs in Medicare in a two-phase program. The first phase would reduce the payment for expensive drugs and increase the payment for inexpensive drugs. The second phase would allow the Centers for Medicare and Medicaid Services (CMS) to use certain value-based tools to pay for drugs in other ways.

ASH has expressed concern about the size and scope of proposed payment cuts, including the potential impact on access to care for patients and encouraged a transparent process in the implementation of the program. The Society’s complete comments may be found on the ASH website at www.hematology.org/Advocacy/Testimony.aspx.

An Early Look at MACRA for Hematology

In late April, CMS released their long-awaited proposed rule for implementing the Medicare Access and CHIP Reauthorization Act (MACRA). The law, passed in April 2015, eliminated annual planned Medicare payment cuts for physicians, replacing it with a system with small predictable updates that are adjusted based on performance. The law also provided a mechanism for physicians to participate in payment models outside of the traditional fee-for-service system. Given the length and complexity of the rule, it will require some time to review and analyze. A few takeaways from the proposed rule are highlighted here; however, given this is a proposed rule, details could change significantly before 2017, when measurement will begin for payment adjustment that begins in 2019.

- **Most physicians will not participate in alternative payment models.** The legislation envisioned a path by which some physicians were able to participate in payment models such as accountable care organizations instead of the current fee-for-service system. However, CMS has proposed to rather rigidly define an alternative payment model and has estimated that more than 90 percent of physicians will not participate in the first year.

- **Quality measurement remains paramount.** While there are technical changes that are important, failure to report on quality measures will still have a deleterious effect on a pay-for-performance score under the new Merit-Based Incentive Payment System (MIPS). CMS proposes to reduce the number of measures required for reporting from nine to six in many circumstances. All of the mechanisms for reporting such as registries and electronic health records are proposed to still be available.

- **Incentive for electronic health record use will be more flexible.** Incentives for the so-called “meaningful use” of electronic health records date back to the stimulus bill passed in the first days of the Obama administration. Since that time, an elaborate series of rules has differentiated health information technology (HIT), requiring certification for the technology and demonstration of certain uses of that technology by the physician practice. Over time, vendors have been unable to keep up with rapidly evolving certification standards that some believe do not reflect the current state of technology. The incentive for HIT use was once a bonus but converted into a penalty in recent years, but remained a measure in which one could either pass or fail, and failure resulted in a Medicare payment cut. CMS now proposes to give partial credit for components of HIT use, which should reduce the number who are penalized.

- **Physicians will have a new reporting burden, but it may be modest.** While most of MIPS is composed of elements of existing programs, the legislation requires assessment of a new category called practice improvement activities. This portion of the MIPS program is an attempt to evaluate and give credit for structures that improve care. CMS proposes a long list of activities (participating in an alternative payment model, being a patient-centered medical home), divided into high and medium value, and proposes to require reaching a score which will likely require reporting on a few activities. Some of these activities may be reported by vendors, and others may be reported by the physician.
Jedi T Cells

Hematology research has become increasingly focused on the study of cellular heterogeneity and parsing out the biologic roles of specific cells. For example, such investigations may explore novel T cell subsets mediating immune responses, distinguish pre-leukemic cells from healthy ones, discover the various roles of un- or multipotent progenitors to the overall contribution of blood production, and identify the specific stromal cells that govern normal or malignant niches. Early on, the microscope was one of the only tools researchers had to study different cells; it was used to make observations regarding cell morphology, nuclear complexity, and differential staining to basic or acidic dyes. The armamentarium has expanded remarkably since then, with a vast array of antibodies that identify unique markers on cells. The tools even allow for flow cytometric techniques such as CyTOF that can identify dozens of markers on a single cell; for genetic mice with gene-specific reporter systems, or for gene-specific Cre recombinase allowing for deletion; and to live in vivo imaging permitting for the direct observation of cells within their natural environment.

The development of these observational tools has also led to the creation of methods to specifically delete a population of cells in a mouse, allowing a researcher to determine specific biologic functions of that cell population in an intact organism. Infusion of an anti-CD8 antibody to remove T cells can be an effective method of cell ablation. However, this requires a unique surface antigen as well as antibodies with predictable pharmacokinetics and in vivo activity. Sometimes the deletion method is as simple as deleting a specific gene which is unique and necessary for a population of cells. Nevertheless, not every cell type can be deleted in this way, and often there are issues with various genes being ubiquitously expressed during embryogenesis, necessitating fixated alleles and more complicated Cre systems. To allow for cell-specific ablation with temporal control, many researchers develop mice in which a cell-specific promoter region drives expression of the diphtheria toxin receptor. When mice are injected with the toxin, the cell type of interest is killed. In many cases, this alleviates concerns over differences in embryonic versus adult organisms and allows for timed ablation of a cell. However, diphtheria toxin administration and death of cells by this manner can cause significant non-specific effects in the mice. In the blood system, both the diphtheria toxin approach and antibodies also have the disadvantage of needing repeated administrations as the cells are rapidly reconstituted.

Recent work from Dr. Judith Agudo and colleagues now adds another arrow in the quiver of cell ablation techniques that may have unique applicability to the field of hematology. They reasoned that T cell–mediated cell ablation would allow for not only cell specificity, but also for a single administration with sustained effects, unlike antibodies or diphtheria toxin. However, making a cohort of T cells for each cell type of interest would not be very practical, so the researchers cleverly chose to generate T cells with a receptor capable of recognizing EGFP-specific MHC I expression. To generate these EGFP-specific T cells, the authors immunized mice with a lentivirus expressing EGFP, and infused them with Jedi T cells to eliminate T cells (Figure). These cells were then used as a nuclear donor for somatic cell nuclear reprogramming, producing what the authors termed just EGFP death-inducing (Jedi) T cells, that will destroy any cell expressing EGFP.

To test these T cells in in vivo systems, the authors used three separate models. First, they used the readily available CX3CR1-GFP mice, which express EGFP in macrophage lineages, including microglia. When Jedi T cells were transferred into these mice, within one week of infusion, all of the microglia were eliminated, which suggests the ability of Jedi T cells to cross the blood brain barrier. However, since EGFP is expressed on macrophages, prior to performing the experiment, the authors irradiated the mice and transplanted them with bone marrow from GFP expressing mice in an effort to restrict EGFP expression to only microglia. Therefore, as the authors state in their manuscript, the effects of irradiation in this model on the integrity of the blood brain barrier cannot be ruled out. However, these studies do demonstrate a remarkable ability for efficient and sustained cell ablation within the brain. The authors then used a Foxp3-EGFP mouse, where regulatory T cells express EGFP, and infused them with Jedi T cells to eliminate Foxp3 T cells. These studies showed robust ablation of the cells, with phenotypes consistent with reports of Foxp3 cell deletion. Finally, to demonstrate the ability to delete a rare population of cells, the authors utilized a hyperpolarization-activated cyclic nucleotide-gated channel (Hcn) EGFP mouse. These cells comprise less than 10,000 of the cells in the heart. Within 10 days of infusion, all of the Hcn+ cells were eliminated, and since they express EGFP, this ablation could be directly visualized and assessed by flow cytometry.

The Jedi mouse could be a remarkable tool to advance hematolgy research. One caveat to this model is that the recognition is restricted to H-2Kd allele, necessitating backcrossing of existing C57Bl/6 strains to either DBA or B10D2 mice. For transplantation studies, or mice with complicated genetics, one could be a barrier to use. Since the cytotoxic T-cell–mediated killing is a natural response of these cells, it is likely that there will be reduced off-target toxicities as compared to diphtheria toxin approaches. Given the abundance of already existing reporter mouse strains that express EGFP, the Jedi mouse and their T cells represent a potentially powerful tool for further cell-specific ablation in hematologic research, supporting studies on the hematopoietic niche, as well as cell-specific immune effects. With the ease of adding EGFP to cancer cell lines, one can envision using these as a method to study T-cell–mediated immune surveillance, or even models of minimal residual disease by tracking remaining EGFP-expressing cells after Jedi T cell infusion.
Understanding Immune Escape in Classical Hodgkin Lymphoma


Morphologically, Hodgkin lymphoma (HL) is characterized by rare malignant Reed-Sternberg (RS) cells surrounded by an ineffective infiltrate of inflammatory and immune cells. Using checkpoint inhibitors to redirect the immune system to eliminate RS cells is an attractive therapeutic approach. Nivolumab and pembrolizumab, the monoclonal antibodies directed against PD-1, demonstrated dramatic activity in phase I studies, with the vast majority of patients with refractory disease responding to therapy. In their recent analysis of tissue biopsies from patients with HL, Dr. Margaretha G.M. Roemer and colleagues elucidate the biologic basis for the impressive activity of immunotherapy in this disease.

The investigators analyzed a cohort of 108 HL patients, all of whom were treated with the Stanford V regimen. The median age was 30 years, and the majority of patients had the nodular sclerosis subtype of the disease. Thirty-three and 41 patients had early-stage favorable (as defined by lack of B symptoms or disease bulk) and unfavorable disease, respectively. Thirty-four patients had advanced-stage disease. Using fluorescence in situ hybridization, researchers assessed alterations in chromosome 9p24, which encodes the programmed death 1 (PD-1) ligands PDL-1 and PDL-2, as well as JAK2 and related transducers and activators of JAK-STAT signaling. Additionally, given the known increased expression of PD-1 ligands in Epstein-Barr virus–positive HL, EBV-encoded RNA (EBER) status was determined. Approximately 60 RS cells per case were evaluated. Compared with the control signal, cases with a 1:1 ratio were categorized as disomic (n=1), and those with a ratio of 1:1 but with more than two copies of each of the PDL-1 and PDL-2 probes were considered polysomic (n=5). Ratios greater than 1:1 but less than 1:3 were labeled as copy gain (n=61) and those cases with greater than 3:1 were classified as amplified (n=39). Two cases harbored translocations. The highest alteration in 9p24 for each case defined the category. Furthermore, the expression of PD-1 ligands was evaluated using immunohistochemical staining (Figure). All cases were concordant for alterations in PD-L1 and PD-L2. Altogether, 107 of 108 cases harbored alterations in 9p24.

The authors correlated clinical risk and genetic alterations with progression-free survival (PFS). As expected, patients with early-stage disease, both with favorable and unfavorable risk profiles, experienced excellent PFS. Patients with advanced-stage disease, however, were more likely to develop recurrent disease. Importantly, outcome was stratified by copy number alterations of 9p24. No relapses occurred in patients with polysomy. The highest relapse rate was seen in those with amplification, and intermediate PFS was observed in the group with copy gains. Additionally, patients with advanced-stage disease were more likely to harbor amplification compared to those with early-stage disease. On multivariate analysis, only stage was predictive of PFS, with a trend for amplification (p=0.075).

These findings elucidate the mechanism underlying the remarkable clinical activity of nivolumab and pembrolizumab in patients with classical HL. Selecting patients with higher risk disease at baseline based on copy number gain, in addition to clinical risk factors, may be important in identifying those patients most likely to benefit from these agents. In turn, this may facilitate further reductions in the use of chemotherapy and radiation, which are associated with late effects in this group of patients who typically experience long term survival.
The management of multiple myeloma has improved enormously over the past 15 years and has turned the diagnosis into a chronic disease for most patients. Several new drug classes have emerged, notably the immunomodulatory agents, proteasome inhibitors, and monoclonal antibodies.

For patients with newly diagnosed disease, the triplet combination of bortezomib, lenalidomide, and dexamethasone has shown excellent activity and is standard of care at many centers. In the setting of relapsed or refractory disease, three new drugs are now being assessed in combination with the backbone of lenalidomide and dexamethasone (Len-Dex). This article reports impressive results for ixazomib, the first of a new class of oral proteasome inhibitor.

The trial recruited 722 patients with refractory, relapsed, or relapsed and refractory disease, and half the patients received Len-Dex with placebo, whereas the rest were given ixazomib at days 1, 8, 15 and 12 of each 28-day cycle.

The main outcome was a nearly six-month improvement in progression-free survival, which increased from 14.7 to 20.6 months with the addition of ixazomib. This effect was observed in all cytogenetic groups, though no difference in survival has emerged at this relatively early stage. The adverse effect profile was remarkably impressive, and thrombocytopenia was the only adverse effect of grade 3+ severity that was increased in the treatment group. Even then, there was no significant increase in bleeding episodes. Peripheral neuropathy has been a major concern with proteasome inhibitors, and although the reported rates were high in both groups, no differences were seen between the two treatment arms.

Ixazomib, lenalidomide, and dexamethasone is therefore a very well tolerated protocol.

This report is one of three recent studies that have used a new agent in combination with a backbone of Len-Dex. Carfilzomib, also a proteasome inhibitor, and the SLAMF7-specific monoclonal antibody eltanizumab have both been assessed in parallel studies. Of interest, all three triplet regimens showed similar efficacy, with an improvement in the hazard ratio to around 0.7 when compared with Len-Dex alone. One aspect that sets ixazomib apart is that it is the first triplet combination that can be completed in one cycle. This, tied with the favorable side effect profile, is likely to establish it as an attractive and convenient regimen for relapsed disease.

Future studies will assess ixazomib as a component of the initial treatment of myeloma.1

We now have three effective triplet combinations for the treatment of relapsed myeloma. Additional agents, such as antibodies that block PD-1-PD-L1 checkpoint signaling or that bind to CD38, have also been under active investigation.2 The ambition, which we can now consider with genuine hope, will be to transform multiple myeloma from a chronic disease into a curable disease.3


Corticosteroids have been a key element of acute lymphocytic leukemia (ALL) induction therapy for decades, yet it has been challenging to reach definitive conclusions about the optimal steroid formulation. Several recent trials have suggested that ALL can have remission induction regimens that do not include corticosteroids. The rationale for using dexamethasone includes greater potency and central nervous system (CNS) penetration, which is particularly appealing in T-ALL, given the higher rates of CNS relapse. However, the use of dexamethasone has been counterbalanced, however, by higher rates of infectious toxicity and treatment-related mortality with dexamethasone-based induction regimens. Past studies have determined that selecting the optimal steroid is complex, and unique features of the patient population and the other components of the treatment regimen influence the optimal induction corticosteroids. Thus, an overarching consensus about the optimal induction steroid has not been reached.

The AIEOP-BFM ALL 2000 trial conducted by the Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP) in collaboration with Berlin-Frankfurt-Münster (BFM) ALL study groups from 2000 to 2006 revisited this question with a randomization between dexamethasone vs. prednisone during the induction phase to determine whether treatment with dexamethasone provides a better event-free and overall survival in newly diagnosed childhood B-ALL and T-ALL. Pediatric patients aged one to 17 years participated in this trial at 127 participating sites in Europe. After receiving a seven-day prednisone prephase, children were randomized to receive either prednisone (80 mg/m²/day) or dexamethasone (10 mg/ m²/day) for an additional 21 days during a four-drug induction with a subsequent taper. A total of 3,720 patients were randomized; 1,853 were assigned to the dexamethasone arm, and 1,867 patients to the prednisone arm.

Post-induction, children treated with malfung chemotherapy for a total of two years or with hematopoietic allogeneic stem cell transplantation in first remission for those with very high-risk features. Prednisone good and poor responses were defined as <1.0 x 10/10L or ≥1.0 x 10/10 peripheral blood blasts, respectively, after the seven-day prednisone prephase. The primary outcome was the dose of methotrexate. The primary end point was the difference in CNS relapse-free survival, with events defined as nonresponse, relapse, secondary neoplasms, or death from any cause. The steroid randomization was halted in October 2004 for patients aged 10 years or older, due to safety concerns.

Strikingly, the overall relapse incidence was reduced by one-third in the dexamethasone arm (10.8% ± 0.7% vs. 15.6% ± 0.9%; p=0.0001), with a proportionally greater reduction in extramedullary versus early bone marrow relapses. However, treatment-related mortality with dexamethasone was significantly higher in the dexamethasone arm (2.5% vs. 0.9%; p=0.0013). Among patients ≥10 years of age, the reduction in relapse risk was offset by this higher incidence of toxic deaths during induction such that no differences in event-free survival were observed in this older age group. On the other hand, event-free survival was significantly better for patients randomized to the dexamethasone arm compared with patients assigned to receive prednisone (83.9% ± 0.9% vs. 80.8% ± 0.9%; p=0.024, respectively).

Among prednisone poor responders, there were no differences in event-free or overall survival or relapse incidence in the randomized groups for either B- or T-lineage ALL. Among the patients with a prednisone good response, a significantly lower incidence of relapse and better event-free survival was observed in the dexamethasone arm compared to the prednisone arm for patients with both B- and T-lineage ALL. In the T-ALL patients with a prednisone good response, relapse rates were notably reduced from 17 percent to 7 percent with dexamethasone as the induction steroid and the better event-free survival of the dexamethasone group also translated into significantly better survival of 91.4 percent ± 2.4 percent compared to 81.7 percent ± 3.2 percent; p=0.003 with prednisone. This survival benefit in the prednisone good response and B-ALL, who had an even inferior, though not statistically significant, survival rate in the dexamethasone group, largely attributable to inferior survival rates following relapse (see Table).

The results of this trial have several important implications for the treatment of B- and T-lineage childhood ALL. The benefits of dexamethasone in reducing relapse rates by one-third were notable given that the induction steroid was the only change in the intensive multi-agent treatment regimen; this intervention has had the largest impact on relapse risk reduction in decades. This benefit, however, was offset by toxicity and treatment-related mortality, especially among patients 10 years or older, which is consistent with the experience of other groups.2 Any benefits of dexamethasone also seemed to be absent in prednisone poor responders, suggesting that a more potent steroid formulation may not be enough to overcome the impact of a steroid-resistant phenotype.

The lack of survival benefit in B-ALL despite an improvement in event-free survival is another key finding, which could be explained by the observation that dexamethasone had the greatest impact in preventing B-ALL relapses that were more readily salvageable, such as extramedullary or later recurrences. These observations highlight the importance of evaluating the extent to which event-free survival benefits translate into improvements in overall survival as well. One of the most notable findings in this report is the benefit for dexamethasone in T-ALL patients with prednisone good responses. Within this subgroup, relapse rates were markedly reduced and event-free and overall survival improved significantly with dexamethasone as the induction steroid. Notably, overall survival rates exceeded 90 percent in this population that has been challenging to treat and salvage at a late stage. Going forward, the results from this trial continue to suggest that there is not a straightforward answer as to whether one steroid is universally superior to another during childhood ALL induction therapy; rather, there are selective benefits to different formulations among patient subsets and a personalization warranted, with emphasis on preventing relapses that cannot be salvaged.


PAUL MOSS, MD, PhD
Dr. Moss indicated no relevant conflicts of interest.

DR. RAOZ, MD
Dr. Raoz indicated no relevant conflicts of interest.

The Hematologist
ASH NEWS REPORTS
The Hematologist: ASH NEWS AND REPORTS

Core Circadian Clock Genes Regulate Leukemia Stem Cells


The circadian rhythm, defined as daily oscillation in various biological processes, is controlled by an endogenous clock in most normal cells in the body. Prior research has established that hematopoietic stem cells (HSCs) are regulated by a circadian rhythm, which is established by cell-autonomous expression of core circadian clock genes as well as by non-cell autonomous inputs from the nervous system and microenvironment. Given the importance of circadian regulation of cell proliferation, there has been great interest in understanding the molecular links between the circadian clock and growth regulation, especially in how this regulation might go awry in cancer. However, research linking circadian rhythm and cancer has been fraught with inconsistencies, including the description of a potential tumor suppressor role that was later disputed by null findings.

Now, Dr. Rishi V. Puram and colleagues have identified a leukemia-specific requirement for core circadian clock genes. This finding came about via an in vivo RNA interference screen in mouse acute myeloid leukemia (AML) cells driven by MLL-AF9. This model is enriched for leukemia stem cells (LSCs), and the authors generated short hairpin RNA (shRNA)–targeting genes encoding 152 DNA-binding proteins that have higher expression in HSCs or LSCs versus myeloid progenitors. Besides confirming the importance of established regulators of LSC function (such as HoxA9 and Meis1), the screen also identified genes encoding the core circadian clock proteins Clock and Bmal1 as among the top-scoring hits. This discovery contrasts previous research that showed that these genes were silenced in leukemia and posits that loss of physiologic circadian rhythm contributes to leukemia development.

The molecular mechanisms regulating the circadian clock involves the asynchronous expression of core clock genes CLOCK and BMAL1, with another set of genes (CRY1, CRY2, PER1, PER2; REV-ERBα, REV-ERBβ) which reciprocally regulate one another in feedback loops (Figure). In addition to validating the requirement of CLOCK and Bmal1 expression in mouse and human MLL-rearranged AML cells, the authors also evaluated the requirement for these genes in normal hematopoiesis. Despite the fact that both normal and leukemia hematopoietic cells have a circadian-dependent regulation of gene expression, Bmal1 was not required for normal adult hematopoiesis in mice.

Given the preferential requirement for circadian clock gene expression in malignant relative to normal hematopoiesis, the authors next tested the effect of a small-molecule REV-ERBα agonist compound in MLL-rearranged leukemia. By stimulating REV-ERB activity, this compound reduced Bmal1 expression as well as the expression of other genes required for MLL-rearranged leukemogenesis (Figure). This drug had a less dramatic effect on CD34+ cord-blood cells, indicating that there might be a therapeutic window for inhibiting the circadian clock machinery in leukemia while sparing normal HSCs.

This work advances the understanding of the role of cell intrinsic circadian rhythm mechanisms in LSCs and normal HSCs. It will now be important to validate the preferential requirement for core circadian clock genes in leukemia not dependent on rearranged MLL as well as primary samples from AML patients with wider genetic backgrounds. Moreover, it will be very interesting to directly compare the circadian rhythms of normal versus LSCs in vivo. However, the models used in this experiment were robust and these experiments set the stage for further research into this area as a novel potential target for anti-leukemic therapy.

Figure

A. Circadian regulation of normal and malignant hematopoietic stem cells

B. Preferential requirement of the core circadian clock genes in leukemic stem cells

Normal and malignant hematopoietic stem cells have circadian-dependent regulation of gene expression but leukemic stem cells in AML require core circadian clock genes. (A) Circadian rhythm is generated by cyclic expression of Bmal1, which is high at the beginning of a subjective day and low at the beginning of a subjective night. When Bmal1 is expressed it forms a heterodimeric transcription factor with CLOCK to directly promote the expression of CRY, PER, and REV-ERBα. CRY, PER, and REV-ERBα then inhibit the expression of Bmal1 and/or the heterorimerization of Bmal1 to CLOCK. (B) The cyclic expression of these genes are present in normal as well as leukemic stem cells in vivo and Puram et al. have now found that Bmal1 and CLOCK are 1) upregulated by the MLL-AF9 fusion oncoprotein and 2) preferentially required in leukemic stem cells over normal hematopoietic stem cells. Moreover, the malignant cells were preferentially sensitive to the compound SRS011, which is an agonist of REV-ERBα and represses Bmal1 expression.

OMAR ABDEL-WAHAB, MD, AND JUSTIN TAYLOR, MD
Dr. Abdel-Wahab and Dr. Taylor indicated no relevant conflicts of interest.

Unique and Paradoxical Functions of the Tumor Suppressor PTEN


PTEN (phosphatase and tensin homolog) is a potent tumor suppressor and plays an important role in regulating the phosphatidylinositol-3 kinase (PI3K) and protein kinase B (Akt) signaling pathway. The development of pre-B cells is tightly controlled and depends on a fine balance of PI3K-Akt activity. A loss of signaling or hyper-activation of the pathway both lead to cell death, whereas an intermediate level of activity allows pre-B cells to pass a tolerance checkpoint that is monitored by PTEN. Point mutations and deletions in PTEN are common in cancer, including hematological malignancies of the T cell lineage and mature B cell lymphomas, implying a tumor suppressor function. To investigate the role of PTEN in immature B cell cancer, Dr. Seyyedeh Shojae and colleagues generated mouse models of pre-B acute lymphoblastic leukemia (ALL) driven by the oncogenes BCR-ABL1 or NRASG12D. Pre-mediated inducible deletion of one or both of the lux-flanked pten alleles in these mice surprisingly preserved malignant transformation and also led to the death of established leukemia cells, indicating that PTEN is required for both the initiation and maintenance of pre-B ALL in vivo. Consistent with these findings, there is no hypermethylation of the PTEN promoter in pre-B ALL patients, resulting in higher levels of PTEN protein and a poor prognosis.

These paradoxical findings prompted reevaluation of genomic data from cancer patients, which confirmed the presence of PTEN mutations in solid tumors and blood cancers, consistent with a tumor suppressor role. However, no point mutations or deletions of PTEN were found in 925 cases of pre-B-ALL, and activating mutations in agonists of the PI3K-Akt pathway were also not present, which supports the experimental mouse model evidence of Dr. Shojae and colleagues. These data suggest that PTEN may have a fundamentally different function in pre-B-ALL than in other hematopoietic malignancies. To elucidate the molecular mechanisms underlying the dependency of pre-B ALL on the presence of PTEN, the researchers used their mouse models to show that deletion of the PTEN gene increased phosphorylation of Akt and the activity of the PI3K-Akt cascade. Additional sophisticated gene manipulation experiments demonstrated that the hyperactive PI3K-Akt pathway triggered a checkpoint to eliminate the leukemic pre-B cells in a manner similar to the removal of auto-reactive B cells. They further showed that the pro-survival function of PTEN is unique to the B-cell lineage and that myeloid cells did not show this dependency.

These findings prompted an investigation of PTEN as a therapeutic target. Using shRNA technology, researchers knocked down PTEN in cells from four patients with pre-B ALL, which caused the death of the leukemic cells, with no effect on the viability of myeloid leukemia cell lines. Similar results were obtained when they performed pre-clinical testing of SF1670, a small-molecule inhibitor of PTEN. However, since PTEN is an important regulator of several cellular processes, as well as a tumor suppressor in other types of cells, adverse effects may be problematic and would require extensive further evaluation prior to the use of PTEN inhibitors in the clinic.

This exciting and important study has revealed a new and unexpected function of PTEN. Contrary to its normal role as a tumor suppressor, PTEN exhibits a pro-survival function that is unique to immature B cells and is required to initiate and maintain pre-B ALL. This dependency of the tumor cells on PTEN may be exploited for therapeutic intervention. The authors propose that targeted inhibition of PTEN and hyperactivation of the PI3K-Akt signaling pathway triggers a B cell tolerance checkpoint whereby auto-reactive B cells are eliminated. This may offer a new strategy to overcome drug resistance in human pre-B ALL.
The hallmark and most common manifestation of sickle cell disease (SCD) is debilitating, severe acute vaso-occlusive pain often resulting in intravenous morphine given continuously for days to weeks. In more than 50 years, there has been no evidence-based strategy for maximizing the management of acute vaso-occlusive pain events in children and adults with SCD. For multiple decades, clinicians have offered nonsteroidal anti-inflammatory therapy, typically ibuprofen, to augment acute pain management without evidence that such treatment attenuates current or future pain events. Platelets have been indirectly implicated in vaso-occlusive events based on their activation markers, including, but not limited to, CD63, P-selectin (CD62), and activated glycoprotein (GPIIb/IIIa). Thus, with the evidence that platelets are activated and mitigate vascular occlusion, the authors postulated that an antplatelet agent that inhibits adenosine diphosphate (ADP) release from activated platelets would decrease the incidence of vaso-occlusive events. Based on a strong biological basis and prior promising results demonstrating a decrease in platelet activation biomarkers, as well as a trend toward decreased pain in a multicenter phase II study of prasugrel (a thienopyridine that inhibits ADP-mediated platelet activation), the investigators pursued a phase III trial.

Dr. Matthew Heeney and colleagues from 51 sites and 13 countries are to be congratulated in completing one of the few international SCD trials that includes participants from the United Kingdom, Africa, Europe, Brazil, and North America. In this phase III trial, a placebo-controlled, parallel-group, multinational clinical trial — the Determining Effect of Platelet Inhibition on Vaso-occlusive Events (DOVE) trial — the investigative team tested the hypothesis that prasugrel is effective in reducing the rate of vaso-occlusive events (pain or acute chest syndrome) in children and adolescents with SCD. Each participant was expected to receive either placebo or prasugrel for at least nine months or a maximum of 24 months. There was a 1:1 random assignment of placebo versus prasugrel (initial dose, 0.08 mg/kg; range, 0.04 mg/kg - 0.12 mg/kg titrated to a predetermined level of platelet reactivity). The trial had several unique components, including assessment with an assay describing the ADP-induced platelet aggregation and the percentage of inhibition. Another novel component was the use of a handheld, mobile electronic patient-reporting device to remind participants and family members to record secondary outcomes, including a diary to document the rate and intensity of pain.

In 27 months, a total of 341 participants were enrolled, exceeding the target enrollment of 220 participants. The trial had a power of 85 percent to detect a 35 percent lower incidence of vaso-occlusive events in the treatment group compared with the placebo group. The primary outcome was that vaso-occlusive events occurred in 2.30 events per person-year and 2.77 events per person-year (rate ratio, 0.83; 95% confidence interval, 0.66 to 1.05; p=0.12) in the treatment group and placebo group, respectively. Similarly, the secondary endpoints did not reveal any evidence that prasugrel was superior to placebo, including assessments for rates of hospitalization, vaso-occlusive events, transfusion, anaphylaxis, use of oxygen, ischemia, and intensity of pain. A major concern in any negative therapeutic trial is that the adherence rate was low; however, the adherence rates were exceptionally high in both groups, 78.2 percent and 81.2 percent in the prasugrel and placebo groups, respectively.

What lessons did we learn from this multinational, randomized controlled trial for an antplatelet agent showing no benefit for the primary endpoint and multiple secondary endpoints? Perhaps the most important lesson is that the international community of families and investigators are eager to participate in a clinical trial attenuating the severity and frequency of pain. Despite being the largest phase III trial ever completed in children and adolescents with SCD, the recruitment goal was reached in 27 months. Another important take-home message is the ability to support adherence to study protocol with an electronic device that prompts family participation. Despite the clear evidence that hydroxyurea therapy decreases vaso-occlusive pain events, only 45 percent of the study population was on hydroxyurea at the time of enrollment. Clearly families of children and adolescents, clinicians, or both, are not enamored with taking hydroxyurea. A better understanding of the barriers for hydroxyurea therapy is needed, as are effective alternatives for this vulnerable population. With the successful completion of the DOVE trial, the SCD community can be optimistic about future phase III trials designed to decrease the frequency and intensity of acute vaso-occlusive events.

Fred Hutchinson Cancer Research Center’s (“Fred Hutch”) Bone Marrow Transplantation Program, one of the largest in the world, had an auspicious beginning. The program predates Fred Hutch itself — bone marrow transplantation as we know it has its roots in the vision and perseverance of one physician scientist, and my former mentor, the late Dr. E. Donnall Thomas. Dr. Thomas came to the University of Washington (UW) from the Mary Imogene Bassett Hospital in Cooperstown, New York, in late 1963. I came to Seattle as a research fellow in 1965, joining a team of bone marrow transplant specialists and a core group of expert nurses. The program was shared among clinicians from the UW and the University of Washington School of Medicine. In 1975, we moved into the current building, the Fred Hutchinson Cancer Research Center, which provided the ever-increasing clinical space for our transplantation patients.

In the early 1960s, the field of clinical bone marrow transplantation was nearly dead. Early reports of human marrow transplantations had failed. All patients had died from complications, most notably from myelosuppression and sepsis without any sign of engraftment. Our laboratory studies at the UW had demonstrated that we could prepare immunosuppressed recipients with antithymocyte serum and then transplant marrow from immunocompetent donors. We were confident that the problem was one of engraftment rather than rejection. However, we were lacking the tools for the preparation of irradiated recipients.

One of the greatest challenges was the preparation of recipient animals to receive the human bone marrow successfully. The team of Dr. George Jones and Dr. A. J. Whitehead had successfully performed transplantations in sheep with irradiated recipients, but they lacked the necessary antithymocyte serum. We were given access to dogs with congenital thymic aplasia, allowing us to develop and implement protocols to prepare irradiated recipients. This was a major breakthrough in the field of transplantation, allowing us to later transplant human bone marrow into irradiated dogs with success.

In the early 1960s, Dr. Thomas moved to the Fred Hutchinson Cancer Research Center, in part thanks to Dr. Donnall Thomas’ relationship with Dr. Bob Hitchcson, who founded the center in his late brother’s name. We abandoned the World War II bunker. The adjacent Swedish Hospital Medical Center provided the ever-increasing clinical space for our transplantation patients.

In those days, everything was new. Dr. Thomas recognized the importance of recruiting different transplant specialists to improve transplantation on multiple fronts. Dr. Dean Buckner led efforts with supportive care. Since the blood center did not provide platelet transfusions, we developed our own transfusion program, which was supervised by Dr. Meera Benaji, with patient families, student volunteers, and on-call UW nurses until the new services of the Seattle Blood Center took over. Dr. John Hansen set up our tissue typing (human leukocyte antigen [HLA] typing) laboratories that continue to this day at the Seattle Cancer Care Alliance, now Fred Hutch’s treatment arm. Dr. Elsbeth E. Secker-Walker led the molecular research of the HLA region and its relation to transplantation outcome. Dr. Thomas recruited the late Dr. Joel Myers, an infectious disease expert from the Centers for Disease Control and Prevention, who laid the groundwork for what is now the largest group of infectious disease researchers of any cancer center. In 1972, Dr. George McDonald joined the team to address gastrointestinal complications of transplantation.

A pulmonary group was also established, led by Dr. David Madtes. Drs. Kenneth Lerner and George Sale established the pathology group which continues at the Seattle Cancer Care Alliance. Pediatrician Dr. Joan Sanders joined our team from Stanford University in 1975 and was instrumental in broadening the application of transplantation to pediatric patients. In the early 1980s, Drs. Thomas’ great niece, Dr. Lilian Gluckman, pioneered umbilical cord blood transplantation after returning to her native France. Dr. Paul Weiden published two pivotal papers in the late 1970s/early 1980s in The New England Journal of Medicine, describing allograft-versus-tumor effects that were instrumental in eradicating the last leukemic cells after transplantation. Dr. Rennata Sandmaier plays a leading role in the mini-transplant effort. Dr. Keith Sullivan, before leaving for the Northwest, more than three decades ago, developed both Fred Hutch’s long-term follow-up group and transplantation for autoimmune diseases — two research areas that he passed up group and transplantation for autoimmune diseases — two research areas that he passed on to his colleagues. As one of them said: “Virtually every major physician trained at Fred Hutch. As one of them said: “Virtually every major field of cancer research is represented here today.” The program now consists of more than 1,000 transplant patients, many of whom have been treated at Fred Hutch.

Our first transplantation did not work. The patient, who had been diagnosed with myelogenous leukemia in blast crisis phase, developed a severe viral infection of a type that we could not have anticipated from our animal work, but we pressed ahead. Today, there are patients still alive for whom we performed a transplantation in 1971 — 45 years ago. In 1972, a young patient with leukemia to whom all the members of our team had grown attached, developed severe acute GVHD after her transplantation. I had conducted research using antithymocyte serum to treat autoimmune disease. Our first transplantation did not work. The patient, who had chronic myeloid leukemia, died from complications, including immune reactions that were not predicted from studies on inbred rodents. Most importantly, however, like humans, dogs develop spontaneous cancers including non-Hodgkin lymphoma, which represented a perfect preclinical disease model for humans, and we learned that.
Is Less in Therapy for High-Risk MDS in the Elderly?

**STUDY TITLE:** A Multi-Center Biologic Assignment Trial Comparing Reduced Intensity Allogeneic Hematopoietic Cell Transplant to Hypomethylating Therapy or Best Supportive Care in Patients w/ Intermediate-2 & High Risk Myelodysplastic Syndrome (BMT CTN #1102)

**CLINICALTRIALS.GOV IDENTIFIER:** NCT0216783

**SPONSOR:** Medical College of Wisconsin

**STUDY DESIGN:** Nonrandomized, multicenter, prospective, comparative biologic assignment

**ACCURAL GOAL:** approximately 400 patients

**PARTICIPATING CENTERS:** 36 study sites in North America

**STUDY SYNOPSIS:** This is a multicenter, prospective trial that compares three-year overall survival and outcomes of older patients with higher-risk myelodysplastic syndromes (MDS) treated with either reduced-intensity conditioning allogeneic hematopoietic stem cell transplantation (RIC alloHCT), or nontransplant therapy or best supportive care. Eligible patients will be 50 to 75 years old individuals who have (or who have previously had) intermediate-2 or high-risk de novo MDS. Patients are deemed suitable candidates for a RIC alloHCT if a matched sibling or matched unrelated donor is identified, with no requirement as to the timing of the transplantation. Patients and physicians must be willing to comply with treatment assignment and have neither intent to proceed with an alternative donor alloHCT not specified in the protocol nor intent to use myeloablative-conditioning regimens.

To reduce enrollment bias and to optimize the control arm, patients who have had tissue typing initiated for an unrelated donor will not be eligible. Patients who have started a sibling donor search or who have found a matched sibling donor are eligible. Importantly, patients may have received prior therapies for the treatment of MDS, including DNA hypomethylating agent-based therapy and cytotoxic chemotherapy.

All subjects are initially assigned to the nontransplant arm and will be reassigned to the transplant arm should a suitable donor (HLA-matched related donor or 8/8 HLA-matched unrelated donor) be identified within 90 days of informed consent. The selection of the RIC alloHCT regimen and nontransplant therapy/best supportive care will be at the discretion of the treating physician. Patients will be evaluated for survival, progression to acute leukemia, and quality of life. Additionally, this study will assess the cost-effectiveness of these two alternative treatment approaches. An important predefined subgroup analysis is to determine the impact of pre-HCT hypomethylating agent-based therapy on study outcomes.

**RATIONALE:** MDS predominantly affects older individuals. Currently, the only potentially curative therapy for MDS is alloHCT. This approach is considered beneficial in a subset of patients with higher-risk MDS (intermediate-2 and high-risk). However, because of the substantial risk of morbidity and nonrelapse mortality associated with myeloablative alloHCT, many patients, especially older patients with comorbidities and poor performance status, are deemed candidates for nontransplant therapy. Alternatively, they are never even referred to a transplantation center for consideration as they are thought to be unlikely to benefit from a myeloablative HSCT. The introduction of reduced-intensity conditioning regimens has expanded the age for alloHCT, though data are limited on its use in MDS. There is a lack of definitive prospective data evaluating the relative risks and benefits of alloHCT compared with nontransplant therapies such as hypomethylating agents, which have been shown to prolong progression-free survival and overall survival in patients with higher-risk MDS. BMT CTN #1102 addresses this knowledge gap.

**COMMENT:** The relative risks and benefits of alloHCT in older patients with higher-risk MDS remain a source of considerable uncertainty. The investigators reasonably expect that most enrolled patients assigned to the nontransplant therapy arm of this study will be treated with hypomethylating agent-based therapies, which have an established therapeutic efficacy in higher-risk MDS and are widely used in clinical practice. By addressing a fundamental question as to whether RIC alloHCT offers a survival advantage compared with this nontransplant therapy among older higher-risk MDS patients who are thought to be transplantation candidates, BMT CTN 1102 has the potential to change practice.

– Sioban Keel, MD

Dr. Keel indicated no relevant conflicts of interest.

Checking Multiple Myeloma with Pembrolizumab

**STUDY TITLES:** A Phase III Study of Pomalidomide and Low Dose Dexamethasone With or Without Pembrolizumab (MK3475) in Refractory or Relapsed and Refractory Multiple Myeloma (Keynote 183); A Phase III Study of Lenalidomide and Low Dose Dexamethasone With or Without Pembrolizumab (MK3475) in Newly Diagnosed and Treatment Naive Multiple Myeloma (Keynote 185)

**CLINICALTRIALS.GOV IDENTIFIERS:** NCT02576977 (in relapsed patients); NCT02579863 (in newly diagnosed patients)

**SPONSORS:** Merck Sharpe & Dohme Corp.

**PARTICIPATING CENTERS:** 33 and more centers in the United States and worldwide (in relapsed patients); 30 and more centers in the United States and worldwide (in newly diagnosed patients)

**ACCURAL GOALS:** 308 patients (in relapsed patients); 640 patients (in newly diagnosed patients)

**STUDY DESIGN:** Both of these trials are phase III randomized studies to evaluate the efficacy or progression-free survival of combining the anti-PD1 monoclonal antibody pembrolizumab with standard immunomodulatory therapy in multiple myeloma (MM) in patients with relapsed/refractory or newly diagnosed disease. In the former study, patients who have had two or more prior lines of treatment and who have been previously exposed to an immunomodulatory drug and a proteasome inhibitor are eligible; these criteria are similar to the U.S. Food and Drug Administration indication for pomalidomide. In the latter study, newly diagnosed patients who are not eligible for autologous stem cell transplantation are eligible. In both studies, pembrolizumab is given 200 mg intravenously every three weeks, with the conventional 28-day immunomodulatory drug schedule: pomalidomide 4 mg by mouth on days 1 to 21 with low-dose dexamethasone (40 mg weekly) in relapsed/refractory patients, or lenalidomide 25 mg by mouth on days 1 to 21 with low-dose dexamethasone.

**RATIONALE:** In cancer initiation and development, tumor cells suppress immune surveillance by using PD-L1 ligand to engage the PD1 receptor on T cells and inhibit T-cell activation (Armand P. Blood. 2015;125:3393-3400). Checkpoint inhibitors targeting PD1 therefore restore T-cell activity against tumor cells and have emerged as a vital new therapeutic strategy. Two anti-PD1 antibodies, nivolumab and pembrolizumab, are now approved in melanoma and lung cancer. The promise of anti-PD1 antibodies is starting to be explored in hematologic malignancies such as Hodgkin disease (Ansell SM et al. N Engl J Med. 2015;373:211-219).

In MM, myeloma cells have increased levels of PD-L1, and the immunomodulatory drugs lenalidomide and pomalidomide inhibit myeloid-derived suppressor cell-mediated immune suppression in vitro (Görgün G et al. Clin Cancer Res. 2015;21:4607-4618). Furthermore, immunomodulatory drugs activate natural killer cells (Hayashi T et al. Br J Haematol. 2005;132:392-393), and they may augment anti-PD1 antibody enhancement of natural killer cell function against MM (Benson Jr DM et al. Blood 2010;116:2286-2292). As a single agent, nivolumab had minimal activity in relapsed MM, with a stable disease rate of 67 percent in a phase I trial; partial responses or better were not seen (Leushin AM et al. Blood. 2014;124:291). However, in combination, two studies presented at the 57th ASH Annual Meeting showed promising results for pembrolizumab with lenalidomide (Sun Miguel J et al. Blood. 2015;126:505) or pomalidomide (Badros AZ et al. Blood. 2015;126:506), both with dexamethasone, in relapsed myeloma. The former trial with lenalidomide demonstrated an ORR of 74 percent in patients with two or more prior lines of treatment. In the latter trial with pomalidomide, the ORR was 50 percent, and these patients were heavily pre-treated, with a median of three prior lines of treatment, and 75 percent were refractory to both immunomodulatory drugs and proteasome inhibitors. In both studies, the treatments were tolerated well, and there were no treatment discontinuations for adverse events.

**COMMENT:** Checkpoint inhibition is emerging as an important new tool in cancer treatment. Its efficacy was first seen in solid tumors such as melanoma and lung cancer, and preclinical work as well as early-stage clinical trials with pembrolizumab in combination with lenalidomide or pomalidomide show auspicious findings for MM. The ongoing randomized studies of pembrolizumab in relapsed and newly diagnosed disease are important studies for validating this type of immunoncology as a novel therapeutic platform in MM.

– Andrea J. Yee, MD, and Noopur S. Raje, MD

Dr. Yee and Dr. Raje indicated no relevant conflicts of interest.
April 21, 2016


In this article, Dr. Kelly McGowan and colleagues report the outcomes and cost-effectiveness of a hospitalwide strategy to replace unfractionated heparin (UFH) with low-molecular-weight heparin (LMWH) for prophylactic and therapeutic indications. They report that the use of LMWH markedly reduces the rate of heparin-induced thrombocytopenia (HIT), with a vast cost savings reflecting decreased HIT-related expenditures. (See Diffusion article on p. 1 by Dr. Adam Cuker.)


Dr. Jennifer Kanakry and colleagues examine the diagnostic power of detection of Epstein-Barr virus (EBV) DNA in plasma versus peripheral blood mononuclear cells to diagnose EBV-DNA. Reviewing results of more than 20,000 samples from a largely immunocompromised hospital population, they report that detection of cell-free EBV DNA in plasma is more sensitive and specific for the diagnosis of EBV disease.

May 19, 2016


Dr. Paul Barr and colleagues report the outcome of a phase II study of the combination of phosphatidylinositol 3-kinase inhibitor idelalisib and the spleen tyrosine kinase inhibitor entospltinib for the treatment of refractory chronic lymphocytic leukemia and non-Hodgkin lymphoma. Although patients had significant responses, the study was terminated early because of treatment-related pneumonitis occurring in 18 percent of patients with two deaths.

May 26, 2016


In their article, Dr. Nicholas Hubbard et al provide an innovative approach for genome editing to knock in a wild-type CD40L and functionally correct disease-causing mutations in a gene in primary human T cells. The level of gene editing seems high enough to potentially allow therapeutic correction of primary immunodeficiency.


In this article, Dr. Aldo Roccaro and colleagues present the possible contribution of the germ line genetic variants LAPTM5+383+7 and ARS5628+80 inherited susceptibility to familial Waldenström macroglobulinemia.


Dr. Marco Heestermans and colleagues examined the roles of platelets, neutrophils and FXIII in a new genetic mouse model of spontaneous venous thrombosis. Their data profoundly challenge the current notions about these players in venous thrombosis.

ASH in Cuba

(Cont. from page 5)

else in society, is exceedingly low and is a major impetus for the exodus of medical trainees to the U.S. and other countries. In 2014, after cutting 100,000 redundant jobs, the Cuban government hired the monthly salaries of nurses and doctors (all amounts are in USD) by 150 percent: from $11 to $25 for entry-level nurses and up to $60 for nurses with the most experience; and from $20 to $30, up to $60 to $70 for the most highly trained specialty doctors.26 Cuba uses its quality doctors, nurses, and ancillary specialists to feed its biggest generator of foreign revenue (roughly $88 billion), the export of some 50,000 medical workers to 66 countries around the world. These overseas postings provide an opportunity for medical professionals to develop increasing expertise in global health, and to earn more income; however, their salaries are often less than what nationals from other countries receive for similar work. In line with Communist Cuba's short-term after the retreat as part of a separate, non-ASH U.S.-Cuba dialogue on health and cancer, sponsored by the American Association for the Advancement of Science (AAAS) and CIM. She had an opportunity to meet with officials from MINSAP, the Dean and faculty of the National School of Public Health, and she toured the National Institute of Oncology of Radiobiology (INOR) with their leadership. INOR is one of the two major tertiary care centers in Havana and specializes in treatment of pediatric and gynecologic cancers. They have radiotherapy facilities including several linear accelerators, and a new PET-CT scanner. Most of the machinery originates from Europe, as do the PhDs earned by their highly educated staff. The Hermanos Ameijeiras Hospital in Cuba is Cuba's major referral center for solid tumor and bone marrow transplantation, with almost 300 transplants performed to date primarily for leukemias, myeloma, and lymphomas. Referrals to such secondary or tertiary care centers originate from so-called local “polyclinics,” which are basic, yet well-staffed primary care doctors' offices that dot Cuba's provinces.

Dr. Shurin came away very impressed with the Cuban infrastructure and personnel. Although the sojourn in Cuba was brief, ASH senior staff and the Executive Committee developed similar impressions, and developed a warm affinity for our brethren Cuban hematologists and the people at large. ASH is energized by the opportunities for clinical and scientific collaboration that lie ahead, especially for trainees, who need only travel 90 miles over the Straits of Florida.

6. Cuba Rises MD’s Salaries by up to 150%. Havana Times, March 21, 2015.

Dr. Gathright wishes to acknowledge the assistance of Drs. Antonio Benceno and Dr. Portifío Hernandez in producing this feature, and Julie Orlando-Castro, ASH’s Director of Education, for serving as a liaison with the Cuban Society of Hematology.

Editors’ Choice

Dr. Bob Lowenberg (Editor-in-Chief) and Dr. Nancy Berliner (Deputy Editor-in-Chief) have combined efforts to identify some of the most outstanding Blood articles that have appeared either in print or online during the two-month interval between issues of The Hematologist. The goal is to underscore the remarkable research that is published in Blood and to highlight the exciting progress that is being made in the field.
Newly Designed ASH Image Bank

The Image Bank is a web-based image library which offers a comprehensive collection of images relating to a wide range of hematologic topics. The new website was launched in March of 2016, containing over 2100 images. Content has been completely reorganized for more logical and intuitive browsing, and includes new images and cases including blood and bone marrow smears with the needed supplemental diagnostic material, as well as a new atlas that demonstrates both normal and abnormal cell morphology and differentiation.

This is a free resource for all to use, and ASH encourages new submissions of high quality, peer-reviewed hematologic images for the Image Bank. For comments, questions, and requests, email imagebank@hematology.org. ASH members can log in to the Image Bank with their standard ASH username and password; non-members must create an account at no cost. Access the Image Bank at imagebank.hematology.org.

Read The Hematologist online at www.hematology.org/thematologist, and catch up on the latest news in the field of hematology right on your desktop, mobile phone, or tablet.