Presenting the Antigen-Presenting Platelet


The role of platelets in mediating inflammatory processes is becoming increasingly recognized.1 Most of the studies in this area have centered on the interaction of platelets with monocytes and neutrophils, but now Chapman et al. in the laboratory of Craig Mornell at the University of Rochester, provide evidence that platelets activate T-cells in an MHC class I-dependent manner. MHC class I molecules are α/β-2-microglobulin heterodimers that are found on the surface of all nucleated cells. During synthesis and transport through the endoplasmic reticulum and Golgi, MHC class I molecules bind to peptides that have been processed from either host or foreign intracellular proteins. At the cell surface, MHC class I molecules present these peptide antigens to T-cell receptor (TCR) molecules by the TCR to produce so-called “signal 1,” a second signal is required for T-cell activation. This process, called co-stimulation, involves engagement of T-cell molecules CD40L and CD82 with antigen-presenting cell receptors CD40 and CD80/86.

Although platelets had not been previously associated with processing or presenting antigen, the authors noted that many of the components required for antigen presentation, including proteasomes and mRNAs for MHC class I subunits, had been identified in platelets.2 Using flow cytometry, they found that murine and human platelets express MHC class I molecules and CD40. Human, but not murine, platelets also expressed CD86. In contrast, MHC class II expression was not detected. Next they studied T-cell activation by measuring IL-2 production or CD69 expression. Murine platelets incubated with intact ovalbumin (OVA) subsequently bound antibody specific for MHC class I–OVA peptide complex, indicating that platelets process and present antigen. Platelets from OVA transgenic (OVA-Tg) mice were used in additional studies. These mice present MHC I–OVA peptides on the surface of all MHC I-positive cells, including platelets. When incubated with OVA-Tg platelets, T cells from transgenic mice bearing TCRs that recognize OVA (OT1 mice) were activated, as judged by increased production of IL-2 and interferon γ, but T cells from wild-type mice were not activated by OVA-Tg platelets. In addition, injection of OVA-Tg platelets into OT-1 mice resulted in increased in vivo production of IL-2 compared with wild-type mice.

The authors then explored the role of platelet MHC class I-dependent events in a model of cerebral malaria produced by infection of mice with Plasmodium berghei. Production of thrombocytopenia using an anti-platelet antibody resulted in decreased production of plasma IL-2 and interferon γ compared with non-thrombocytopenic controls. Additionally, platelet MHC class I expression was increased in mice infected with P. berghei. Mice also were infected with a transgenic variant of P. berghei that expresses an OVA peptide. Infected red cells from these mice were incubated with OT-1 T cells and with platelets from either wild-type or MHC class I-deficient mice. T-cell activation was observed with wild-type platelets, indicating that platelets can process and present parasite-derived antigen to T cells in an MHC class I-dependent manner.

Finally, the authors used the transgenic variant of P. berghei to explore a cell-based vaccine strategy for prevention of malaria. Platelets from wild-type or MHC class I-deficient mice were incubated with an OVA peptide and then injected intravenously into wild-type mice on days one and 10. The mice were then challenged with a lethal dose of P. berghei on day 21. There was a significant increase in survival of mice immunized with wild-type platelets compared with MHC class I-deficient platelets. Additionally, the mice immunized with OVA-treated, wild-type platelets showed both decreased parasitemia and increased OVA-specific cytotoxic (CD8+) T-cell response.

The study by Chapman et al. provides evidence for the novel hypothesis that platelets participate in the initiation of immune responses. Platelet antigen presentation may be an important mechanism to combat infectious agents but may also contribute to pathologic vascular inflammation.

The Hematologist: Why is it important for members to donate to the Foundation?

Dr. George: If we are serious about curing blood diseases, we must ensure that there is a pipeline of new, talented hematology researchers and clinicians available to build on the remarkable advances that have already been made. While the Society has been able to provide seed money for programs that support the next generation of physician scientists and basic researchers, more needs to be done. That means that the hematology community must unite in support of these essential programs.

Dr. Bradner: “Community” is exactly the right word. This isn’t about just one aspect of hematology; this is about the current and future state of research, practice, and the next generation of students, trainees, and junior members.

The Hematologist: What are the programs that the Foundation will fund?

Dr. George: The programs that the Foundation will focus on are those that are essential but do not generate self-supporting revenue. ASH needs a funding source to sustain programs for training its junior members and for supporting them as they begin their careers. Training and early-career support are at the heart of the matter for me, because we are a community in crisis, at risk of losing many talented investigators and clinicians who make our field so dynamic.

Dr. Bradner: This overview of the ASH Foundation simply marks the start; we will continue to identify innovative ideas to address current and future concerns of the hematology community. As the challenges and opportunities in science and medicine are changing so rapidly, we must adapt as we address these issues and identify new needs.

I think it is important for donors to realize that 100 percent of their gifts given through the ASH Foundation will be spent directly on these programs, because ASH will be providing both start-up and ongoing funds in support of these programs and will continue to cover all of the administrative and management costs associated with both the programs and the ASH Foundation.

The Hematologist: What does the work of the Foundation mean to you?

Dr. George: The Foundation gives me comfort knowing that all of my donation will be spent on the wonderful programs ASH has developed to support and advance the careers of its members. The Foundation provides the promise that our established programs will endure, and it gives us the opportunity to do things we haven’t done before.

(Cont. on page 3)
Learn About the Best From the Best at the 2013 Highlights of ASH®

Listen to hematology experts provide in-depth and unbiased analyses of leading research and clinical updates presented at the 54th ASH Annual Meeting. Enjoy opportunities to learn new practice strategies and discuss patient cases with colleagues and experts through panel discussions and other speaker-attendee interactive activities. Whether you are unable to attend this year’s annual meeting and want to get an update on the latest findings in clinical research in the field or you want to meet and network with your colleagues, you should take advantage of this opportunity.

To better meet the needs of hematologists worldwide, ASH is bringing this informative program to eight locations across North America, Asia, and Latin America. Choose the location and date that is the most convenient for you, and plan ahead to attend the only official highlights of the 54th ASH Annual Meeting.

Get the most recent information about the meetings at www.hematology.org/highlights.

The ASH Foundation

(Cont. from page 2)

The Hematologist: What inspires you to give?

Dr. Bradner: We have reached a pivotal moment in hematology, where the promise of new innovation is threatened by economic constraints. These same financial constraints apply to individuals who need to know that their unsellish contributions will be allocated expertly, efficiently, and transparently. Donors should expect that contributions will be spent solving important problems. Personally, ASH has supported key aspects of my professional training, education, and now independent research in drug discovery. I contribute to ensure that the next generation of hematologists will enjoy the same catalytic opportunities.

The Hematologist: What would you say to your fellow members?

Dr. Bradner: Please consider the ASH Foundation as a major step forward for the Society. We welcome any contribution of resources to programs that support hematology. Please go to www.hematology.org/foundation and provide much-needed resources to programs that support hematology. Get the most recent information about the meetings at www.hematology.org/highlights.

How to Donate

It’s the time of year when many individuals give generously in support of programs that are personally meaningful. As you plan your year-end giving, we ask that you please make a donation to the ASH Foundation and provide much-needed resources to programs that support hematology. Please go to www.hematology.org/foundation, and donate today.
Mantle cell lymphoma (MCL) is a rare type of lymphoma, representing about 6 percent of all cases of non-Hodgkin lymphoma. Median age at diagnosis is 68 years, and the vast majority of patients are diagnosed with advanced-stage disease. Patients with MCL typically present with asymptomatic disease, there is no survival disadvantage to expectant management. For those requiring therapy, patients may be divided into categories of young and fit (≤ 65 years without significant comorbidity), or older (> 65 years with inability to tolerate high-dose therapy).

Younger and Fit Adults With MCL

Although the addition of rituximab (R) to conventional chemotherapy regimens has significantly improved prognosis in nearly all subtypes of B-cell non-Hodgkin lymphoma, its addition to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) in MCL has not translated into improved outcomes. The German Low Grade Lymphoma Study Group found that, due to the short durability of the response, R-CHOP compared with CHOP did not improve progression-free survival (PFS) despite an improvement in overall response rate (94% vs. 75%).

Given the disappointing outcome with R-CHOP therapy alone in younger patients, emphasis has been placed on intensification of induction therapies and consolidation strategies with high-dose therapies followed by autologous stem cell rescue (ASCR).

A randomized trial comparing myeloablative radiochemotherapy and ASCR versus maintenance interferon-α in patients ≤ 65 years achieving a partial or complete response with CHOP-like induction, with or without rituximab, demonstrated an improved PFS in the radiochemotherapy arm (median PFS of 39 months vs. 17 months) though there was no OS difference. This study is the basis of adoption of high-dose therapies and ASCR as consolidative strategies in younger patients. The Nordic Lymphoma Group in the MCL2 study adopted a cytarabine-containing induction regimen consisting of six cycles of dose-intensified CHOP alternating with high-dose cytarabine with rituximab in cycles two through six, followed by high-dose therapy (HDT) and ASCR. The four- and 10-year PFS were highly encouraging at 73 percent and 55 percent, respectively. An improved median event-free survival of 83 months was also recently reported by the French group in a phase II trial using an induction regimen consisting of three cycles of CHOP and three cycles of rituximab with DHAP (dexamethasone, high-dose cytarabine, and cisplatin) followed by HDT and ASCR.

Another approach to increase the durability of remission in MCL patients employs the use of intensified doses of chemotherapy including cytarabine without stem cell transplantation. A phase II trial of R-HyperCVAD (rituximab, fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) by the MD Anderson group showed a high complete remission rate of 87 percent and three-year failure-free survival of 64 percent. However, this therapy has significant toxicity with 8 percent treatment-related mortality. Also, a preliminary report of the regimen used in the cooperative group setting by the Southwest Oncology Group demonstrated a less favorable outcome. Therefore, this therapy should be reserved for young and fit patients with close monitoring for toxicity. Finally, a comparative effectiveness study from the NCCN NHL database comparing initial MCL therapy in younger patients demonstrated that R-CHOP alone was inferior to aggressive therapies such as R-HyperCVAD or R-CHOP followed by HDT and ASCR.

In general, we favor an aggressive treatment approach consisting of an induction regimen followed by HDT and ASCR for patients who are ≤ 65 years without significant comorbidity. The optimal induction chemotherapy has not been established, and options include standard or intensified R-CHOP with or without the addition of cytarabine-containing regimens. An ongoing intergroup, randomized phase II study comparing R-HyperCVAD versus R-bendamustine followed by HDT and ASCR in MCL patients ≤ 65 years will contribute to the identification of the optimal induction chemotherapy.

Older Adults With MCL

The use of dose-intensified, cytarabine-containing induction regimens followed by HDT and ASCR is not feasible for most elderly patients due to excessive toxicity. Therefore, treatment strategies focus on regimens that improve PFS while minimizing toxicity.

Results of a double randomized trial comparing R-CHOP versus R-FC (rituximab, fludarabine, and cyclophosphamide) in patients > 60 years who were ineligible for HDT, with second randomization of responders (complete or partial response) to either maintenance rituximab or maintenance interferon-α showed a clear OS benefit as well as less toxicity for R-CHOP compared with R-FC. The remission duration was also doubled in the maintenance rituximab versus the interferon-α arm. Furthermore, among patients who had a response to R-CHOP induction, maintenance rituximab significantly improved OS when compared with maintenance interferon-α (4-year OS, 87% vs. 63%), while it had no influence in the group that received R-FC induction. Given these compelling data, we favor R-CHOP therapy followed by maintenance rituximab as an upfront therapy in older patients with MCL.
The role of R-bendamustine has also been explored in the treatment of MCL. Preliminary results from a randomized controlled trial by the German Low Grade Lymphoma Study Group comparing R-bendamustine versus R-CHOP in indolent B-cell NHL or MCL (MCL made up 18% of total cohort) demonstrated better tolerability of R-bendamustine and a significant 20-month improvement in PFS over R-CHOP, but there was no OS improvement. Based on these preliminary data, R-bendamustine can be considered in older patients, especially when there is concern for the tolerability of a more aggressive treatment regimen. An ongoing U.S. Intergroup randomized phase II trial in older MCL patients is comparing bendamustine with rituximab with or without bortezomib, with a second randomization to maintenance rituximab with or without lenalidomide.

Interest in developing new approaches to treatment of MCL, including Bruton tyrosine kinase (BTK) and PI3 kinase inhibitors, remains high. But presently, a careful approach that incorporates available trial data in the decision making process should be used in selecting upfront therapy for patients with MCL (Figure).


Dr. Odejdje and Dr. LaCasse indicated no relevant conflicts of interest.
Congress to Tackle Funding Cuts During “Lame Duck” Session; NIH Funding in Jeopardy

Prior to adjourning for the November elections, Congress approved a six-month continuing resolution (CR) to keep the federal government running through March 27, 2013. The CR provides funding for most government agencies, including the National Institutes of Health (NIH), at fiscal year 2012-enacted levels plus a temporary 0.6 percent across the board increase.

However, the CR does not alter the sequester (additional across-the-board cuts mandated by the Budget Control Act of 2011), meaning that without congressional action before the end of the calendar year, discretionary programs such as NIH will face significant funding cuts on January 2, 2013. According to a report issued by the White House Office of Management and Budget in September, NIH would be subject to cuts totaling 8.2 percent as part of the sequester. This draconian measure means that as many as 2,300 NIH grants could be eliminated.

It is critical that all Members of Congress hear from ASH members about the impact that inadequate funding has on medical research and the need for our lawmakers to take a balanced approach to reducing the deficit that doesn’t further cut NIH and other core federal programs. To take action, please visit the ASH Advocacy Center page (grassroots.hematology.org) and join ASH’s campaign by sending an email to your Senators and Representative.

Take Action to Help ASH Fight for NIH Funding

The Society is working hard to let Congress know that sequestration must be averted, but we need your help! Visit www.hematology.org/FightNow for a list of easy and meaningful actions you can take to make your voice heard about the impact that inadequate funding has on medical research and the need for Congress to take a balanced approach to reducing the deficit that doesn’t further cut NIH and other core federal programs.

Tell ASH Your Story

Have a story to tell about how NIH funding affects your career and your concerns about upcoming cuts to NIH funding for hematology research? Please share it with ASH at www.hematology.org/FightNow. We need your stories to fight for hematology funding!

Physicians Face 27 Percent Medicare Payment Cut January 1

Physicians are scheduled to receive a 27 percent cut from Medicare reimbursement beginning January 1, 2013, unless Congress takes legislative action to prevent it. ASH strongly opposes the proposed cuts to physicians and has long advocated for repeal of the flawed sustainable growth rate formula that mandates the reductions. ASH advocates for replacement legislation that would recognize the real-world need for an adequate and stable physician payment system.

ASH strongly believes the solution to this physician payment problem is to replace permanently the current payment formula with a system that keeps pace with the cost of caring for our nation’s seniors and that does not threaten the viability of physician practices. Continuing the stop-gap approach of enacting temporary patches serves no one well.

However, a major barrier to reforming physician reimbursement is the cost of repealing the current payment formula. Most Members of Congress have indicated that they strongly oppose the potentially devastating cuts. The challenge does not lie in convincing Congress that the program is ill-conceived, rather the problem is finding a way to pay for maintaining Medicare reimbursement at the current level. To do so will require that lawmakers cut spending elsewhere or locate “offsets” to cover the loss of grant that NIH would otherwise accrue to the budget by reducing Medicare reimbursement rates. The Congressional Budget Office has estimated that a one-year patch to block the scheduled cut in physician Medicare payment rates would require offsets totaling $18.5 billion over 10 years, while a permanent solution would cost tens of billions of dollars more.

The cost of a permanent solution is expensive and the details of the fix will be complex, requiring time, debate, and compromise to work out. Consequently, the Society is advocating for Congress to pass a statutory payment update when it returns in November, before cuts take effect again, that lasts at least through the end of 2013.

All Members of Congress need to hear from their physician constituents about the need to avert the scheduled physician payment cut. ASH has developed an online advocacy campaign so hematologists can easily contact their Members of Congress and share their concerns. Please visit the ASH Advocacy Center page (grassroots.hematology.org) to participate in the Society’s online advocacy campaign today.

NIH Names New Director of National Center for Advancing Translational Sciences

National Institutes of Health Director Francis S. Collins, MD, PhD, has appointed Christopher P. Austin, MD, as director of the National Center for Advancing Translational Sciences (NCATS). Dr. Austin succeeds Thomas Insel, MD, who had been serving as NCATS Acting Director since the Center’s establishment in December 2011.

A developmental neurogeneticist by training, Dr. Austin earned his undergraduate degree in biology from Princeton and his medical degree from Harvard. He completed clinical training in internal medicine and neurology at the Massachusetts General Hospital and a fellowship in genetics at Harvard. Dr. Austin began his NIH career in 2002 as senior advisor to the director for translational research at the National Human Genome Research Institute. His other NIH roles include serving as director of the Therapeutics for Rare and Neglected Diseases program and the National Chemical Genomics Center, and as scientific director of the Center for Translational Therapeutics. Since the NCATS launch in December 2011, Dr. Austin had served as director of the program’s Division of Pre-Clinical Innovation.

In mid-September, 27 ASH members from across the country gathered in Washington, DC, for the ASH Advocacy Leadership Institute (ALI). Participants brought a range of interests and perspectives to the two-day workshop and met with representatives from more than 40 congressional offices to discuss the devastating impact that potential funding cuts would have on NIH-supported hematology research.
More people in low- and middle-income countries die from cancer than from HIV, TB, and malaria combined, and two-thirds of the global cancer deaths occur in these nations.1, 4 Hematologic disorders contribute to a significant portion of these deaths, and, in fact, the incidence of non-Hodgkin lymphoma in most countries in Africa is two to five times higher than in the United States, according to the International Agency for Research on Cancer. Innovation is needed to address disparities in care that contribute to the observed major differences in survival in low- and middle-income countries when compared with resource-rich nations.

One model of intervention developed in response to this challenge involves collaborations between institutions in resource-abundant and resource-limited settings — referred to as “twinning.” St. Jude Children’s Research Hospital pioneered many of the approaches that this model as part of their International Outreach Program (IOP), which is currently active in 14 countries. One of their first twinning relationships was established with the Instituto Materno Infantil de Pernambuco (IMIP) in Recife, Brazil, where, in 1993, they helped establish standard treatment protocols for childhood acute lymphocytic leukemia (ALL). As seen in Figure 1, prior to the partnership, the event-free survival rate for children with ALL was less than 50 percent and eight years later was approaching that of resource-abundant nations at greater than 80 percent.1 With the goal of further improvement in outcome, the hospital in Recife has sustained those survival figures while treating about 80 cases per year.4

An effective twinning collaboration such as this requires: 1) identifying people and institutions at both sites who are willing to make a long-term commitment to the process, 2) developing a long-term plan with regularly scheduled evaluations to enable necessary programmatic adjustments, 3) developing a cancer center of excellence with physicians and staff dedicated to oncologic care, and 4) enabling patient consultations between the two sites, usually through the use of Web-based conferencing, that involve physicians, nurses, pharmacists, and other clinic staff. Additional details on implementing twinning programs can be found in the online guide available on the St. Jude IOP website at www.jsiro.org/international/.

Funding for the entire IOP at St. Jude utilizes approximately 1 percent of the institution’s budget.4 Annual costs for each twinning program range from $200,000 to $208,000 for each of the first five years with the distribution of the cost responsibility shown in Figure 2, illustrating that nearly 90 percent of these costs are covered by government funding and support from non-governmental organizations (NGOs). Recent estimates suggesting that $131 billion could be saved globally each year through appropriate cancer care and prevention in low- and middle-income countries have made it more attractive for local governments and NGOs to invest in these programs. These projected savings result from the prevention of lost economic production associated with the morbidity and mortality of cancer diagnoses.4

That rapid, accurate diagnosis is a key to improved outcome in the management of many hematologic malignancies is illustrated in acute promyelocytic leukemia (APL), a potentially curable disease that can be diagnosed quickly and definitively (using molecular techniques to identify the pathognomonic t(15;17)), and because APL is associated with significant early mortality if aggressive, supportive care measures to manage the bleeding complications caused by APL-associated disseminated intravascular coagulation are not rapidly implemented, this disease was targeted by ASH when the Society launched its initial foray into global health care. Beginning in 2004, ASH, through its International Members Committee, developed the International Consortium on Acute Promyelocytic Leukemia (IC-APL) that involved hematologists in Brazil, Mexico, Uruguay, and Chile. The goal of the IC-APL was to use available local laboratory and medical resources to identify patients with a suspected diagnosis of APL, rapidly confirm the diagnosis using molecular techniques through a centralized laboratory, and initiate therapy quickly.

Prior to this initiative, the overall survival rate for patients with APL in Brazil was 53 percent. Subsequent to implementation of IC-APL in Brazil, a two-year overall survival rate of 80 percent has been reported in the 97 evaluable patients who were enrolled in the program.5 Based on the success of this project, an ASH-sponsored program designed to provide support for management of other types of acute leukemia (in addition to APL) in these countries is under development, and this new, broader initiative will operate as the International Consortium on Acute Leukemia (ICAL).

Crucial to the success of IC-APL was the ability of the local hematologists to use fundamental hematologic skills, clinical laboratory film and bone marrow morphologic interpretation, to identify those patients who might have APL. It is those basic skills that have been targeted for improvement in the several international locations being covered by ASH since 2007 in partnership with Health Volunteers Overseas, a nonprofit organization dedicated to improving global health through education. Hematologists working at sites in Uganda, Cambodia, and Peru vary in their diagnostic abilities, and they have asked for programs to improve their skills, as they appreciate that this is the first step to improving treatment and management of hematologic diseases. This assessment applies not only to malignant diseases such as ALL and APL, but also to non-malignant hematologic disorders including sickle cell anemia, thalassemias, and even iron deficiency anemia.

Key technologies that assist with these successful collaborations include using Web-based conferencing, recording and sharing clinical data between sites through the use of the Pediatric Oncology Network Database (POND), and making other information accessible to international providers on websites such as St. Jude’s www.carekids.org. Web-based care-case conferences between partners enable timely pre-treatment consultations. However, studies show that even with this relationship, the frequency with which these consultations change management declines, suggesting that this model has an educational component that leads to clinical independence.8

With the completion in 2009 of a submarine cable system, Internet connectivity was improved and expanded in large parts of Eastern and Southern Africa, making it possible to view educational case conferences and share diagnostic images between Fred Hutchinson Cancer Research Center in Seattle and the Uganda Cancer Institute in Kampala. As with any health-related intervention, reliable data are required to measure the impact of twinning relationships. The POND is a centralized server used by multiple international programs including those of St. Jude’s twinning initiatives and ASH. This technology was designed to allow rapid translation of a database to other languages while preserving a standard format so that data can be compared and followed concurrently in different countries. This standardization also allows accurate analysis of research on outcomes and provides a mechanism for measuring the impact of ongoing improvement projects.

While these technologies can play a large part in improving care, they are ineffective without also addressing the barriers to care faced by patients in low- and middle-income countries, including difficulties with transportation, cost of care, inadequate nutrition, and limited access to medications and diagnostic tools. Twinning relationships improve patient care, education, and teaching at both of the partnering institutions. The need to address disparities in health care is great, and pioneering programs such as those initiated by ASH and St. Jude Children’s Research Hospital have established a framework that can be built upon by other institutions and organizations to improve global health through support, service, and education.
Patients with multiple myeloma (MM) usually respond favorably to initial therapy and experience a prolonged period of progression-free survival (PFS). However, the disease invariably recurs, and time to relapse shortens with successive treatments. Ultimately, the disease becomes refractory to therapy. The median survival time for patients with MM is in the range of five to seven years, with a median time from diagnosis to first relapse of approximately three years. Clearly, there is a need to improve treatment of relapsed disease with a goal of improving survival. To address this issue, the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation initiated a prospective, multicenter, phase III study comparing the efficacy and safety of a triple combination (thalidomide and dexamethasone [TD]) in patients with MM progressing or relapsing after treatment with high-dose chemotherapy and autologous stem cell rescue. Overall, 269 patients were randomly assigned to receive either bortezomib (1.3 mg/m² intravenously) or no bortezomib in combination with thalidomide (200 mg per day orally) and dexamethasone (40 mg daily for 4 days every three weeks). Treatment cycles were 21 days, and the duration of treatment was one year. The bortezomib was given twice weekly for two consecutive weeks (days 1, 4, 8, and 11) followed by a 10-day rest period for the first 8 cycles (6 months). Subsequently, the schedule of bortezomib was days 1, 8, 15, and 22 followed by a 20-day rest period (42-day cycle) for 4 cycles over a total of 6 months. Overall, the complete response plus near-complete response rate was significantly higher (45% vs. 25%; p=0.001), and the median duration of response was significantly longer (172 vs. 13.4 months; p=0.003) with VTD compared with TD. The median time to progression (a primary endpoint of the study) was significantly longer with VTD, 19.5 versus 13.8 months; p=0.001. However, with a median follow-up of 30 months, there was no survival difference between the two groups. Toxicity was greater with VTD compared with TD, especially the incidence of peripheral neuropathy, 41 percent versus 18 percent, respectively. More importantly, the incidence of grade 3 and worse neuropathy was significantly higher in the VTD cohort compared with the TD, 31 percent versus 14 percent (p=0.001). The authors also reported higher rates of grade 3 or worse infectious complication and thrombocytopenia in the VTD arm. Thus, the three-drug regimen was more effective than the two-drug regimen in the treatment of MM at first relapse after high-dose chemotherapy followed by autologous stem cell rescue, but the VTD regimen was associated with a significantly worse toxicity profile than the TD regimen with no survival difference observed between two regimens.

When used as initial treatment for MM, VTD has demonstrated a high complete response rate and prolonged PFS in patients with either standard or high-risk genetic features. Additionally, the use of the VTD combination in the post-transplantation setting induced molecular responses in a subset of patients, many of whom experienced long periods of treatment-free remission. The current study shows that response rates and PFS are significantly better with the three-drug regimen than the two-drug regimen, but overall survival between the two study arms was not significantly different, and the toxicity profile of the three-drug regimen was unfavorable compared with that of the two-drug regimen. The higher incidence of grade 3 or worse neuropathy in the VTD-treated group is likely a consequence of concomitant use of thalidomide and bortezomib. The next generation of immunomodulatory drugs and proteasome inhibitors will almost certainly replace thalidomide and bortezomib, respectively, and the toxicity profiles of the newer combinations will likely be more favorable than their older counterparts. A more favorable toxicity profile would increase enthusiasm for a triple-drug regimen, but an impact on overall survival would really make three the magic number.

Another NOTCH: Splenic Marginal Zone Lymphoma Sequenced


Marginal zone lymphomas are interesting in their pathogenesis, with several of the extranodal types related to chronic infections, such as H. pylori, B. burgdorferi, and C. psittaci. Splenic marginal zone lymphoma (SMZL) shows some linkage to hepatitis C infection, but only in a minority of cases as the incidence is low even in regions where hepatitis C infection is relatively prevalent. The molecular events underlying this generally indolent illness are incompletely characterized. Uncommonly, for a low-grade lymphoma, alkylating agents are relatively ineffective treatment, which is possibly linked to the high rates of TP53 deletion observed. The therapeutic approaches most often used are rituximab, alone or in combination with cytotoxic agents, or splenectomy. No potentially helpful targeted agents have been suggested until now, as molecular characterization of the pathobiology of SMZL has been impeded by the relative rarity of the disease.

A collaborative group composed of researchers from the University of Eastern Piedmont in Novara, several other Italian centers, and the group at Columbia University, and another collaborative group made up of researchers from the University of Michigan and other North American centers used whole-genome sequencing to identify patterns of mutation in a small number of cases. The Italian group also used copy-number analysis to highlight the major areas of gain or loss of chromosomal DNA. Both groups used Sanger sequencing to confirm their findings in a larger cohort; the results are broadly similar. The most notable finding was the frequent mutation in the NOTCH-2 gene, in a region that results in loss of the C-terminal PEST domain, thereby impairing proteosomal degradation of the truncated protein. This abnormality was present in 20 to 25 percent of SMZL cases, but very few other lymphoma types, and is thought to result in upregulation of the NOTCH pathway. Interestingly, in a smaller number of cases, the Italian group also found genetic lesions in other components of the NOTCH pathway, such as NOTCH-1, SPEN, and DTX1, suggesting convergence of the mechanisms of pathogenesis. They also identified less frequent mutations in genes regulating chromatin remodeling and transcription, and B-cell receptor signaling, as have been described in other low-grade B-cell lymphomas.

There was an interesting divergence between the two studies when the clinical significance of the NOTCH-2 mutation was investigated, with the Italian group concluding that mutant cases had a better overall survival, but the Michigan group finding that mutant cases were more likely to undergo recurrence, transformation, and fatal progression. It seems likely that selection bias influenced these findings, but there is clearly more work to do in understanding the significance of mutations of this gene in the progression of lymphoma.

The NOTCH pathway shows a high degree of evolutionary conservation and is responsible for regulating many developmental decisions, such as hemopoietic lineage identity, as well as differentiation and tissue homeostasis. This diverse developmental regulation includes the formation of the B-cell marginal zone in lymphatic tissue and the maturation of the antibody repertoire. Apparently, NOTCH-2 is not sufficient for malignant transformation, since patients with the Hajdu-Cheney syndrome, which is caused by NOTCH-2 germline mutations similar to those described in SMZL, do not show an increased incidence of lymphoma, although they do experience severe progressive bone loss. The frequent occurrence of activating mutations in SMZL does, however, suggest that to prevent clonal escape the NOTCH pathway might be a target for intervention perhaps in combination with inhibitors of the other relevant pathways. In this context, use of inhibitors of the NF-κB pathway or of B-cell receptor signaling would seem a logical next step in combination with a NOTCH inhibitor. Given the generally slow pace of progression, it may be that such an approach could be successful in controlling the disease over long periods of time.

The Hematologist: ASH NEWS AND REPORTS
A Temporal Role for Hepcidin in the Anemia of Inflammation and Chronic Disease


The anemia of inflammation and chronic disease (AICD) is usually a slight to moderate, hypoproliferative, normocytic anemia. Patients with AICD are often elderly or chronically ill, and the non-severe anemia can worsen co-existing cardiac, pulmonary, and vascular maladies. Some severe or prolonged AICD cases can be microcytic as a consequence of functional or absolute iron deficiency. Recent AICD studies have appropriately focused on hepcidin, the liver peptide hormone that restricts both dietary iron absorption by duodenal enterocytes and iron recycling by macrophages through the binding and down-regulation of ferroportin, the surface membrane iron exporter. Transgenic mice engineered to overexpress hepcidin have several of the features associated with AICD including anemia, hypoferrremia, and iron-restricted erythropoiesis.

However, the hepcidin transgenic mouse erythrocytes are microcytic rather than normocytic, and hepcidin transgenic mice do not have increased inflammatory cytokines or relatively decreased erythropoietin concentrations that have been associated with AICD in patients and in some animal models. Using a model of AICD in mice in which the experimental animals received serial turpentine infections to induce subacute abscesses, Prince et al. demonstrated normal hepcidin expression, serum iron concentrations, and transferrin saturation in a chronic-phase, normocytic anemia that was associated with increases in neutrophils, platelets, interleukin-6, interleukin-1β, and intracellular reactive oxygen species (ROSs) in erythroid precursors and erythrocytes.

Although this serial-abscess model had previously demonstrated a rapid induction of hepcidin expression and hypoferrremia in the first few days of abscess formation, erythrocyte sizes in the chronic-phase anemia varied between normocytic and microcytic. Using larger numbers of mice, Prince et al. demonstrated that the increase in hepcidin expression and hypoferrremia observed in the acute phase resolve within three weeks, but slight, normocytic anemia persisted. During the chronic phase, both hepcidin expression and serum iron concentration were normal, despite a persistent elevation of interleukin-6, a known, potent inducer of hepcidin expression. Erythropoietin levels were slightly increased whereas AICD is characterized by relatively decreased erythropoietin production. The serial-abscess mice had an increased proportion of early-stage erythroblasts compared with control mice, and reticulocyte numbers were also very slightly increased. While consistent with increased erythropoiesis and erythropoiesis, these results suggested a shortened erythrocyte life span, but erythrocyte lifespan was found to be normal. Ineffective erythropoiesis related to ROS-related damage was hypothesized to account for the observed increase in early-stage erythroblast production.

In the serial-abscess model, Prince et al. have demonstrated a slight, chronic, normocytic anemia with increased neutrophils and platelets that is similar to the laboratory profile observed in many patients with AICD, but unexpectedly the chronic anemia was not accompanied by increased hepcidin expression or hypoferrremia. The acute response to abscess formation does increase hepcidin expression and induce hypoferrremia, but both hepcidin expression and serum iron concentration normalize in the chronic phase, indicating that other factors other than hepcidin maintain the chronic anemia. Because many different chronic diseases are associated with AICD, the role of hepcidin expression will likely vary considerably, playing a larger role in those anemias with hypoferrremia and microcytosis but having a lesser or only temporary role in anemias that are normocytic and have more normal serum iron values. Understanding the factors responsible for AICD as well as the period during which each factor has its greatest effect should provide more specific approaches to treatment of AICD, when it becomes symptomatic.


Leukemia: Watch Out, Get De(re)ressed!


Survival rates in patients with acute myeloid leukemia (AML) are low, especially in the elderly (median survival < 1 year) in whom the disease is most common. Moreover, treatments are toxic, confining patients to hospitals and requiring frequent clinic visits. Thus, new approaches to treatment are needed to improve both outcomes and quality of life. With these issues in mind, an international team of investigators led by Arthur Zelent from the Institute of Cancer Research, UK, has tackled the question of how to induce leukemia cells, which are arrested at an immature stage, to differentiate. The inspiration for these studies came from the success of all-trans-retinoic-acid (ATRA) in the treatment of acute promyelocytic leukemia (APL). Outcomes using ATRA for APL elegantly demonstrated that differentiation-based therapy can have a high “therapeutic index,” meaning the therapeutic agent produces significant benefit with little toxicity. ATRA has been tried unsuccessfully in the treatment of other subtypes of AML. Therefore, Zelent’s group set out to characterize the mechanism by which AML cells resist ATRA-induced differentiation and in the process showed that the resistance to differentiation can be reversed by using a commercially available antidrugs.

Leukemic blasts are characterized by increased proliferation and lack of differentiation. These qualities are acquired through both genetic and epigenetic mechanisms. Epigenetic changes include modifications of DNA and histones (complexes of proteins that comprise the nucleosomes of chromatin that packages DNA). Different histone modifications support either gene expression or repression. For example, dimethylation of histone H3 at lysine 4 (H3K4me2) is observed in the promoter region of actively expressed genes, and expression of these genes is turned off (repressed) by lysine-specific demethylase 1 (LSD1) that converts dimethylated H3K4 (H3K4me2) to mono- (H3K4me1) or unmethylated H3K4. Of relevance to the current study, transglutaminase (TGP), an LSD1 histone demethylase inhibitor, is marketed as an antiproliferative and is available commercially.

For ATRA to be effective it must bind to its nuclear receptor called retinoic acid receptor (RAR), and the ATRA/RAR target genes must be in the “on” position so that expression can be induced by the ATRA/RAR transcription factor complex. Prior studies have shown that some ATRA-responsive genes are inactive in leukemia as a consequence of histone modification. In the current study, Schenk and colleagues used ATRA in combination with LSD1 inhibitors to induce differentiation by derepressing epigenetically silenced genes. Synergy between ATRA and LSD1 inhibitors (including TGP) to induce myeloid differentiation of several leukemia cell lines was observed in vitro. To determine whether the combination might be therapeutic in “real-life” AML, Schenk et al. assessed the effect of ATRA/TGP in primary AML cells from three patients using a murine xenotransplant model. They reported that pretreatment of AML samples with ATRA/TGP followed by in vivo administration of the drugs after leukemic cell injection prevented AML expansion. Importantly, there was no effect of ATRA/TGP on engraftment of normal cord blood, suggesting that this combination therapy would likely have a favorable therapeutic index. To test the capacity of ATRA/TGP to treat leukemia once it has developed (mimicking the clinic situation), primary AML samples from the three patients were injected into mice and allowed to expand for 15 days. Administration of ATRA/TGP significantly reduced the tumor burden in each of the three leukemic mouse models. Interestingly, in two of these AML models, ATRA alone had an effect similar to the ATRA/TGP combination.

To investigate the hypothesis that TGP paves the way for ATRA to activate gene expression by histone modification, the investigators assessed how the combination of ATRA/TGP affects gene expression and H3K4 methylation. A strong correlation was observed between gene expression and H3K4me2 in promoter regions of specific genes of which (e.g., CD11b, CD11c, and CD8) are associated with myeloid differentiation.

This exciting preclinical study suggests that epigenetic modifiers in combination with differentiation therapy may be an effective approach to treating AML. We anticipate that additional preclinical studies will further characterize the basis of the resistance to ATRA-induced differentiation and thereby provide the underpinning for the optimal use of this low-toxicity approach to the treatment of AML. In this way, the depression surrounding AML treatment may be mitigated by derepression.
An Updated Risk Model That Improves Prognostic Forecasting in Myelodysplastic Syndromes


A few (relatively) fortunate souls with the lowest-risk disease subtypes of myelodysplastic syndromes (MDS) are likely to be alive a decade after diagnosis and are unlikely to ever progress to acute myeloid leukemia (AML), while those unlucky individuals with the highest-risk forms of disease have a life expectancy measured in months. Because the outlook for different patients with MDS varies so dramatically, prognostic tools are important to aid management decisions.

Currently, the MDS risk-stratification model most widely used in clinical practice and for clinical trial eligibility determination is the 1997 International Prognostic Scoring System (IPSS), which incorporates marrow blast proportion, marrow karyotype, and the number of peripheral blood cytopenias into a four-tier system that is predictive of survival and AML progression risk. In the last five years, investigators at MD Anderson Cancer Center developed two improved MDS risk models—a general scoring system for all MDS subtypes and another tool specific for IPSS lower-risk disease—while European investigators proposed and subsequently modified a World Health Organization (WHO) classification-based Prognostic Scoring System (WPSS). The MD Anderson risk models and the WPSS offer some improvements on the IPSS and complement the WHO MDS classification.

Now, 15 years after the original IPSS appeared, a large international effort coordinated by Peter Greenberg of Stanford University and sponsored by the nonprofit MDS Foundation has culminated in a Revised IPSS (IPSS-R, Tables). The IPSS-R is based on a 7,015-patient dataset, pooled from databases in 11 countries. While the IPSS-R score is generated with the same three components as the original IPSS—marrow blasts, karyotype, and cytopenias—the IPSS-R includes a broader range of abnormal karyotypes and weighs cytogenetic results more heavily than the original IPSS did, since recent data from a large German-Austrian and MD Anderson-merged cytogenetic database indicate that the karyotype is more important than the blast proportion in determining MDS risk. Other major revisions include divide of marrow blasts into five scoring groups (since 4% blasts are not really normal), inclusion of scores for each individual cytopenia (with minor weighing by degree of cytopenia), and expansion from four to five risk tiers. Although the IPSS-R is too complex for all but mnemonist savants to memorize, several online calculating tools and mobile apps are already available to assist hematologists who have more typical neurobiology. (Check out www.mds-foundation.org/ipss-r-calculator.)

The IPSS-R offers several advantages that should facilitate its immediate acceptance as the heir apparent to the IPSS. Increased sensitivity to the degree of thrombocytopenia is a clear enhancement, as severe thrombocytopenia is an IPSS-independent risk validated by several independent post-IPSS analyses. Although many MDS-associated karyotypes are observed so rarely that they could not be included in the IPSS-R and remain of unclear prognostic importance, the 15 most common abnormalities are incorporated, including IPSS-opaque recurrent anomalies such as isolated del(1q) or del(12p). These changes appear to be clinically relevant: Using the IPSS-R resulted in re-categorization of 27 percent of IPSS lower-risk patients into higher-risk groups, while 18 percent of higher-risk patients were “upgraded” to a better outlook.

However, even though it represents an advance, the limitations of the IPSS-R suggest that it is likely to be a transitional tool. Like the original IPSS, the IPSS-R is only valid in adults with de novo disease at the time of diagnosis, which excludes patients with therapy-related MDS, children, and previously treated patients. The IPSS-R also does not capture the kinetics of the disease; the patient who had a normal blood count earlier in the year for an insurance examination and now has severe pancytopenia and 11 percent blasts is likely to be in a worse position than the patient with equivalent blood counts who in retrospect had eight years of mild macrocytic anemia, was never completely evaluated, and whose other counts have been slowly dwindling over the last two years.

Furthermore, neither the IPSS-R nor any of the other major risk models adequately capture the severity of patients’ comorbid conditions, which for many elderly patients are a more important determinant of life expectancy than their MDS. It is not clear whether chromosomal abnormalities detected by FISH or array-based techniques have the same implications as those included in the IPSS-R, which is based on standard G-banded karyotyping. Finally, the IPSS-R includes no molecular markers. Certain MDS-associated somatic mutations have prognostic value independent of any of the existing models, and understanding these is the pathway forward in MDS risk assessment. Of note, the mere presence or absence of mutations may not provide enough information; allele burden is also likely to be clinically relevant.

Because of these limitations and the current pace of advancement in the field, it seems unlikely that the IPSS-R will be obsolete in 15 years before “IPSS Version 3.0” will debut. Still, the IPSS-R is a helpful advance based on a large amount of work using a database more than 8 times larger than that used for the original IPSS. This fundamental risk model will undoubtedly evolve and improve with inclusion of molecular markers and other variables. No prognostic model can provide a perfect prophecy about the appointed time of a patient’s death—not, given human nature with its abhorrence of determinism and individual psychologic need for exceptionalism, would we want it. Prognosis also is intimately dependent on available therapies, and new drugs that can change the natural history of the disease may invalidate prognostic scoring systems: Remember that once acute promyelocytic leukemia was the deadliest form of AML, and then along came all-trans-retinoic acid and arsenic trioxide, which changed everything.


Table

<table>
<thead>
<tr>
<th>Revised IPSS (IPSS-R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk group</td>
</tr>
<tr>
<td>Very good</td>
</tr>
<tr>
<td>Good</td>
</tr>
<tr>
<td>Intermediate</td>
</tr>
<tr>
<td>Poor</td>
</tr>
<tr>
<td>Very poor</td>
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<table>
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<tr>
<th>Parameter</th>
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<th>Good</th>
<th>Intermediate</th>
<th>Poor</th>
<th>Very poor</th>
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<tbody>
<tr>
<td>Cytogenetic risk group</td>
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<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Marrow blast proportion</td>
<td>0%</td>
<td>1-2%</td>
<td>3-5%</td>
<td>6-10%</td>
<td>&gt;10%</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10-10.9 g/dL</td>
<td>&lt;10 g/dL</td>
<td>&lt;8 g/dL</td>
<td>&lt;6 g/dL</td>
<td>&lt;5 g/dL</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>0.8 x 10^9/L</td>
<td>&gt;0.8 x 10^9/L</td>
<td>&gt;1.5 x 10^9/L</td>
<td>&gt;5 x 10^9/L</td>
<td>&gt;20 x 10^9/L</td>
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<tr>
<td>Platelet count</td>
<td>100-100 x 10^9/L</td>
<td>&gt;100 x 10^9/L</td>
<td>&gt;50 x 10^9/L</td>
<td>&gt;30 x 10^9/L</td>
<td>&gt;20 x 10^9/L</td>
</tr>
</tbody>
</table>

JASON GOTLIB, MD, MS
Dr. Gotlib receives clinical trial funding from Incyte, Inc., Braftac Therapeutics, and YM Biosciences. He also serves on an advisory board and receives honoraria from Incyte, Inc.

MUCH has been learned after five years of phase II clinical trial experience with several JAK2 inhibitors in treatment of myelofibrosis, as well as the two phase III COMFORT trials that led to approval of ruxolitinib in 2011.1,2 Some tyrosine kinase inhibitors (TKIs) in this drug class are relatively more JAK2-specific (e.g., SAR302503, formerly TG101348), whereas others demonstrate inhibitory activity against both JAK1 and JAK2 (e.g., ruxolitinib and CYT387).1-3,4 Inhibition of JAK2 blocks JAK-STAT-mediated cellular proliferation of myeloproliferative neoplasm (MPN) cells, whereas inhibition of both JAK1 and JAK2 is felt to be responsible for interrupting the aberrant cytokine signaling that contributes to disease features such as hypercatabolic constitutional symptoms, ineffective hematopoiesis, and bone marrow fibrosis. JAK inhibitors have produced substantial clinical improvement on two fronts: reduction of splenomegaly and amelioration of debilitating constitutional symptoms. However, on-target, anti-proliferative effects may mitigate these benefits and sometimes limit dosing of these agents in certain situations (e.g., inducing anemia and thrombocytopenia). With only modest or no effects on JAK2 V617F allele burden and bone marrow fibrosis, and uncertain impact on long-term survival, today’s JAK inhibitors do not share the exceptionalism of imatinib and the next generation TKIs used to treat CML. The genetic complexity of MPNs and the lack of specificity of current JAK inhibitors for mutant JAK2 account for some of these differences in efficacy.

Disease persistence on JAK2 inhibitor therapy, or what I refer to as “disease creep,” is not an uncommon circumstance, and it usually manifests over time as a gradual return of splenomegaly and/or constitutional symptoms (in contrast to the more rapid return of symptoms within approximately one week after drug hold/discontinuation). The lack of in-depth clinicopathologic responses with JAK2 inhibitors is also synonymous with the concept of disease persistence. Dr. Koppikar and colleagues from Dr. Ross Levine’s laboratory at Memorial Sloan-Kettering Cancer Center convincingly demonstrate that one mechanism of disease persistence relates to reactivation of JAK2 via transphosphorylation by JAK family members JAK1 and TYK2.

To unravel the biology of disease persistence, investigators first exposed different JAK2 V617F-positive cell lines to ruxolitinib or a pre-clinical phase JAK inhibitor for several weeks and found that chronic exposure to these drugs resulted in continued proliferation and resistance to apoptosis at concentrations that prevented growth of the parental cell line. Cells were also resistant to other JAK inhibitors (e.g., SAR302503) to which they hadn’t been exposed. Sequencing of the JAK2 gene in persistent cells revealed no acquired resistance mutations akin to the BCR-ABL resistance mutations observed with TKIs in CML. In contrast to the observed inhibition of downstream signaling in untreated cells or treatment-naive MPN patient samples exposed to JAK2 inhibitors, persistent cell lines and granulocytes from patients on chronic ruxolitinib therapy displayed sustained phosphorylation of JAK2 and signaling intermediates, such as STAT3, STAT5, and MAP kinase. A consistent finding in the persistent versus treatment-naive cells or patient samples was the increased association between phosphorylated JAK2 and JAK family members JAK1 and TYK2. In addition, increased JAK2 mRNA expression and increased stability of the JAK2 protein was found to contribute to persistence and to facilitate heterodimerization formation between JAK family members. Withdrawal of JAK2 inhibitor treatment resulted in re-sensitization to different JAK inhibitors and loss of association of JAK2 with JAK1/TYK2. Knockdown of JAK1 and TYK2 reverted cells from a persistent to sensitive phenotype. An Hsp90 inhibitor that degrades JAK2 and a type II JAK inhibitor that also binds inactive JAK2 were found to retain the capacity to inhibit persistent cells to the same degree as naive cells, suggesting that alternative treatment approaches may be able to bypass the persistence phenomenon.

These data highlight that reactivation of JAK2 via heterodimerization with JAK family members is a fundamental basis of MPN disease persistence in patients on JAK inhibitor therapy. Syncopated schedules of JAK inhibitor monotherapy with the intent of re-sensitizing patients to drug is unlikely in patients on JAK inhibitor therapy. Syncopated schedules of JAK inhibitors is a fundamental basis of MPN disease persistence in the setting of JAK2 inhibitor therapy.

Binding of thrombopoietin (TPO) to its receptor (MPL) leads to phosphorylation of JAK2, activation of the JAK-STAT pathway, and increased cellular proliferation (A); JAK2 inhibitors block phosphorylation of JAK2 and reduce cellular proliferation and as well as other signaling cascades (B). One mechanism of disease persistence in the setting of JAK2 inhibitor therapy is re-phosphorylation of JAK2 through its heterodimerization with JAK family members JAK1 and TYK2. The result is re-activation of the JAK-STAT pathway and downstream signaling events, including cellular proliferation (C).
Approximately 20 to 25 percent of those with an unexplained venous thromboembolism (VTE) experience a recurrence within five years of the initial event. If it was possible to predict those at risk for recurrence, then, in the absence of unacceptable bleeding risk, anticoagulation might be continued "long-term," rather than for the three to six months recommended in the ESH/ESC 2012 guidelines. Determining optimal duration of anticoagulation, however, is challenging, as VTE recurrence declines and bleeding risk increases over time. Further, while individual VTE recurrence risk can be estimated based on individual risk factors (e.g., sex or D-dimer), the relationship to bleeding risk, on an individual basis, is unknown as clinical trials have been insufficiently powered to generate evidenced-based recommendations.

To address this problem, Tosetto and colleagues conducted a meta-analysis on pooled data from seven large prospective clinical trials that involved 1,818 patients with unprovoked VTE treated for a minimum of three months with a vitamin K antagonist. Comparing predictors of VTE recurrence and anticoagulation bleeding data, they modeled recurrence risk using Cox regression coefficients to develop a VTE recurrence prediction score. The study was limited to unprovoked proximal VTE or pulmonary embolism, excluding thromboembolic events that occurred during the puerperium period or in the setting of trauma, surgery, immobilization, cancer, or pregnancy. Patients using hormonal therapy at the time of VTE and those with thrombophilia were included, as hormonal therapy is considered a weak risk factor for VTE, and thrombophilia was considered a weak risk factor for recurrence.

For each individual subject, a VTE recurrence score was calculated based on a sum of scores of four predictors: age, sex, hormone use at the time of the VTE, and D-dimer measured three weeks after stopping oral anticoagulation. The final prognostic score was based on regression coefficients for each predictor (Table). A score of +2 was assigned for abnormal D-dimer, +1 for age < 50 years old, +1 for male sex, and -2 for hormone use at onset of VTE (among women), generating a $DASH_2A_1S_1H_2$ score. Therefore, for individuals with an initial unprovoked VTE and a DASH score < 1, the annual VTE recurrence risk is 3.1 percent (Table), which justifies stopping anticoagulation after three to six months, assuming (based on approximation of the annual bleeding incidence) that a VTE recurrence rate of less than 5 percent is an acceptable risk. In contrast, a DASH score > 2 is associated with a VTE recurrence risk of 6.4 percent or higher, a risk level sufficiently high to warrant prolonged anticoagulation if the bleeding risk is acceptable.

Tosetto and colleagues have developed a simple prediction score for VTE recurrence based on D-dimer, age, sex, and hormone use at the time of the VTE. The authors suggest that approximately half of patients with unprovoked VTE and a DASH score < 1, the annual VTE recurrence risk is 3.1 percent (Table), which justifies stopping anticoagulation after three to six months, assuming (based on approximation of the annual bleeding incidence) that a VTE recurrence rate of less than 5 percent is an acceptable risk. In contrast, a DASH score > 2 is associated with a VTE recurrence risk of 6.4 percent or higher, a risk level sufficiently high to warrant prolonged anticoagulation if the bleeding risk is acceptable.

**DASH Prediction Score Derived From Cox Regression Analysis**

<table>
<thead>
<tr>
<th>DASH Predictors</th>
<th>β coefficient</th>
<th>p-value</th>
<th>Recurrence Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer abnormal after AC</td>
<td>0.96</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Age &lt; 50 yr</td>
<td>0.43</td>
<td>0.002</td>
<td>1</td>
</tr>
<tr>
<td>Sex - male</td>
<td>0.58</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Hormone use at VTE onset</td>
<td>-1.05</td>
<td>0.002</td>
<td>-2</td>
</tr>
</tbody>
</table>

**DASH Prediction Rule**

DASH Score

- **≤ 1.0**: Recurrence Rate 3.1%, 6.4%, 12.3%
- **> 3.0**: Recurrence Rate

with a DASH score of 2 or higher, prolonged anticoagulation appears to be indicated, as long as bleeding risk is acceptable. Limitations of the study include short follow-up (22 months), short duration of anticoagulation (6 months), and selection of subjects taking warfarin-only anticoagulation. Notably, this prediction score reflects data from study subjects receiving warfarin anticoagulation. Thus, it would be of interest to develop a recurrence risk score using data from patients receiving low-molecular-weight heparins or the newer oral anti-thrombin and anti-Xa inhibitors. For women with unprovoked VTE, the reason estrogen was associated with a two-fold lower VTE recurrence rate is unclear, given this prediction score reflects data from study subjects receiving warfarin anticoagulation. Thus, it would be helpful to reassess the prediction score using data from patients receiving different types and doses of hormonal agents.

Clinical Trials Corner

Oral Proteasome Inhibitors in Multiple Myeloma

**STUDY TITLE:** A Phase 3, Randomized, Double-Blind, Multicenter Study Comparing Oral MLN9708 Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Relapsed and/or Refractory Multiple Myeloma

**SPONSOR:** Millennium Pharmaceuticals, Inc.

**CLINICALTRIALS.GOV IDENTIFIER:** NCT01564537

**PARTICIPATING CENTERS:** 8 centers throughout the United States

**ACCRUAL GOAL:** 703 patients

**STUDY DESIGN:** An estimated 703 patients with relapsed and/or refractory multiple myeloma (MM) will be enrolled. They must have received one to three prior therapies, have disease that is not refractory to lenalidomide or proteasome inhibitor therapy, and have adequate cardiac, pulmonary, renal, and hepatic function. Patients in the experimental arm will receive MLN9708 (4 mg orally) on days 1, 8, and 15 along with lenalidomide (25 mg) on days 1 through 21 and dexamethasone (40 mg) on days 1, 8, 15, and 22 every 28 days until disease progression. Patients in the placebo comparator cohort will receive a placebo on days 1, 8, and 15 along with lenalidomide (25 mg) on days 1 through 21 and dexamethasone (40 mg) on days 1, 8, 15, and 22 every 28 days until disease progression. Primary endpoint is progression-free survival (PFS), and secondary endpoints include overall survival (OS), rate of complete and very good partial response, duration of response, time to progression, safety profile, pain response, change in global health status, OS and PFS in the high-risk population, and pharmacokinetic data.

**RATIONALE:** This clinical trial will compare the PFS in patients with relapsed and/or refractory MM receiving either MLN9708 or placebo, in each case combined with lenalidomide and dexamethasone. Therefore, this clinical trial is a new drug registration trial that attempts to build upon the PFS benefit of lenalidomide in combination with dexamethasone, an FDA-approved regimen in this patient population.

**COMMENT:** The use of proteasome inhibitors and immunomodulatory drugs has transformed MM therapy and patient outcome. In particular, the combination of bortezomib and dexamethasone has shown efficacy in the treatment of relapsed, refractory, and newly diagnosed MM. Similarly, the combination of lenalidomide and dexamethasone has shown efficacy in the treatment of relapsed and refractory as well as newly diagnosed MM. Apparently because of synergistic cytotoxicity, the combination of lenalidomide, bortezomib, and dexamethasone can achieve responses in 60 percent of patients whose MM is refractory to either lenalidomide or bortezomib alone. When used as initial therapy, this combination regimen achieves responses universally, with 74 percent of patients having a very good partial response or better and 52 percent having complete and near complete responses, including molecular complete responses. The second generation proteasome inhibitor carfilzomib has recently been approved for treatment of patients who have received at least two prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy. Already the combination of carfilzomib, lenalidomide, and dexamethasone has shown remarkable activity in relapsed MM, providing the basis for a recently fully-enrolled phase III clinical trial comparing carfilzomib, lenalidomide, and dexamethasone with the standard lenalidomide/dexamethasone combination.

MLN9708 is an oral chymotryptic proteasome inhibitor, which in preclinical studies triggers activation of caspase 8 and 9, upregulation of p21, induction of ER stress response, downregulation of NF-kB, inhibition of angiogenesis, and activity in a xenograft murine model of human MM. In phase I clinical trials, the maximum tolerated dose (MTD) was established at 4 mg. Neurotoxicity was not observed and adverse effects were minimal ( Rash, GI toxicity). MLN9708 has a half-life of four to six days and is given either weekly or twice weekly. In early clinical trials, MLN9708 has been combined with lenalidomide/dexamethasone and this combination produced significant responses both in relapsed and newly diagnosed MM. Therefore, this current phase III randomized trial compares combined lenalidomide, dexamethasone, and MLN9708, predicated upon synergistic preclinical cytotoxicity and promising clinical activity, with lenalidomide/dexamethasone for new drug approval in relapsed MM. For the first time, it will define the efficacy and tolerability of an all-or-none regimen incorporating immunomodulatory drug and proteasome inhibitor combination therapy. Moreover, although this trial focuses on patients whose MM is refractory to either MLN9708 or placebo, in each case combined with lenalidomide/dexamethasone, this combination is also being studied as both initial and maintenance therapy.

— Kenneth C. Anderson, MD

Dr. Anderson has served on advisory boards for Celgene; Millennium: The Takeda Oncology Company, and Onyx.

Personalized Kinase Inhibitor Therapy for Patients With AML

**STUDY TITLE:** A Phase II Pilot Study of Kinase Inhibition in Relapsed/Refractory Acute Leukemias: Using a Comprehensive In Vitro Kinase Inhibitor Panel to Select Individualized, Targeted Therapies

**CLINICALTRIALS.GOV IDENTIFIER:** NCT01620166

**STUDY SPONSOR:** Oregon Health & Science University (OHSU) Knight Cancer Institute

**COLLABORATORS:** National Cancer Institute, Bristol-Myers Squibb

**PARTICIPATING CENTER:** OHSU

**ACCRUAL GOAL:** 24 patients

**STUDY DESIGN:** Leukemia cells from patients over 21 years of age with relapsed/refractory disease after at least one cycle of salvage therapy will be tested to evaluate sensitivity to a panel of kinase inhibitors. Based on those results, one of the study’s FDA-approved drugs (dasatinib, nilotinib, sorafenib, or sunitinib) is selected for treatment of each individual patient. A change in leukemic burden over time is the primary endpoint. The underlying concept is that the kinase inhibitor screen targets leukemia cell function that is a property distinct from conventional classification strategies based on karyotype, cell count, and molecular markers. Although the available drug panel is small, the trial will help identify new therapeutic targets and permit monitoring of kinase pathway activation.

**RATIONALE:** Effective options for treatment of refractory or relapsed AML and ALL are limited, especially for older patients who often have co-morbid conditions that compromise performance status. With median survival in elderly patients of about 10 months for AML and five months for ALL, alternatives to high-toxicity, cytotoxic chemotherapy regimens are needed. Leukemogenesis is frequently driven by aberrant kinase signaling, and the successful treatment of BCR-ABL kinase expressing CML with imatinib provides a blueprint for combining leukemia eradication with minimal toxicity. However, unlike CML, acute leukemias are genetically and functionally heterogeneous, with no single signaling pathway dominating. The tyrosine kinase inhibitor screen used in this trial targets the majority of the tyrosine kinase and identifies at least one effective FDA-approved kinase inhibitor in 35 percent of relapsed patients.

**COMMENT:** Owing to pathobiologic heterogeneity, developing effective, minimally toxic treatment regimens for patients with acute leukemia remains an unmet challenge. The mainstay of current treatment for acute leukemia is combination cytotoxic therapy using a “one-size-fits-all” format. Drug development and approval processes are slow and expensive. Moreover, interventional drug trials are population-based, leaving little room for individualized approaches. Struggling with a wide spectrum of drug treatment responses, several leukemia study groups have attempted to tailor treatment based on measures of minimal residual disease (MRD). By their very nature, such trials are reactive whereby the MRD marker tracks patient response in vivo, and MRD failure prompts a treatment change to a potentially more suitable drug. Such an approach comes at a cost of months of drug exposure that can induce drug resistance and promote clonal evolution. Despite the exciting discovery of tyrosine kinase signaling pathways, identification of specific targets within these pathways, and development of narrowly targeted and well-tolerated drugs, AML and ALL patients have benefited little from these accomplishments. Leukemia cell kinase signaling pathway activity can vary between disease subtypes, over time, within clones, and, importantly, among individual patients. As knowledge of leukemia signaling abnormalities has grown, clinical trial design has not always kept up. The current trial aims to move innovative bench approaches more seamlessly to the bedside, thereby enabling a more personalized approach to the treatment of acute leukemia. In contrast to simple MRD approaches, the failure of a drug to kill a patient’s leukemia cells is revealed in vivo, combining the advantages of choosing the most promising drug with the appeal of tracking disease response directly.

While this is an early-phase pilot trial, the kinase inhibitor screen in combination with an innovative trial design may help translate our understanding of leukemia biology into treatment approaches that address the individual needs of patients with acute leukemia.

— Peter Kurre, MD

Dr. Kurre works at Oregon Health & Science University, which is the study sponsor and participating center of this trial.
The ASH Clinical Research Training Institute: A Personal Success Story

JOSEPH MIKAEL, MD, ME
Consultant Hematologist, Mayo Clinic Arizona, Associate Professor, Mayo College of Medicine

Editor’s Note: 2012 marks the 10-year anniversary of the Clinical Research Training Institute (CRTI). In the September/October issue of The Hematologist, articles that focused on the history, productivity, and direction of the program were published in recognition of this milestone in the history of ASH’s flagship training program. The current article is a continuation of the 10-year anniversary celebration and spotlights a successful mentoring relationship that came out of the Institute.

When Dr. Tanya Wildes was selected as a member of the CRTI class of 2011, she had no idea of the profound impact the program would have on her career path. Following completion of fellowship training in hematology/oncology and geriatrics, Tanya knew she wanted to devote her career to studying older adults with multiple myeloma, but she was struggling to formulate a plan to achieve that aim. After completing the CRTI training week in La Jolla, CA, she returned to her home institution with a clear vision of how to proceed both with her research project and her career development. The CRTI experience provided Tanya with the academic tools and the confidence to seek extramural funding for her project, and this past summer, she received an NIH R03 award through the Grant for Early Medical and Surgical Subspecialists’ Transition to Aging Research (GEMsSTAR) Program to support her project titled "Pilot Study of Geriatric Assessments in Senior Adults with Multiple Myeloma.”

Tanya identified the CRTI small-group sessions and the yearlong mentoring program as pivotal to her success. Small-group sessions take place daily for three to five hours during the intense one-week summer session and consist of three to four attendees, two to three CRTI faculty members, and a biostatistician. The intent is to individualize feedback to the attendees focusing on both their research projects and their career development. In Tanya’s case, the small-group mentoring sessions made her think through her research question in a way that led directly to the idea for the R03 project. Her initial CRTI project was designed as a retrospective study aimed at comparing outcomes between older adults with multiple myeloma who underwent high-dose therapy and autologous stem cell rescue with those who did not. Her small-group mentors, Dr. John Leonard, Dr. Scott Gitlin, Dr. Sarah Vesely, and I, helped illuminate the limitations of this approach, identifying confounding elements that would limit interpretation of the data. We provided guidance in the restructuring of the research question that allowed for data evaluation using the statistical technique of comparative effectiveness analysis. In this case, the focus was on identifying the characteristics of older adults with multiple myeloma who underwent treatment with induction chemotherapy followed by autologous stem cell rescue. These data would then provide the basis for properly matching the control group.

The small-group discussions, coupled with didactic seminars dealing with research design, provided Tanya with the background necessary to develop a model that would yield valid, interpretable results. Drawing from her training as a geriatrician, Tanya recognized that common geriatric problems, such as functional impairment, fall history, cognitive decline, comorbid conditions, and polypharmacy, likely impacted a clinician’s decision to offer aggressive therapy. Using her CRTI experience, Tanya developed a pilot project in which she proposed a prospective cohort study to examine comprehensive geriatric assessment as a predictor of treatment strategy for older adults with multiple myeloma. This pilot project served as the basis for her successful R03 application.

Another pivotal moment during her CRTI week was the day her small-group mentors asked each trainee to review their career-development plans. With an objective view of her career goals, her mentors focused on areas that needed additional attention. In particular, it was clear that her clinical work and her research program were not well aligned. She was not formally part of the myeloma clinic, although her research involved patients with myeloma. With her small-group mentors’ support and with the assistance of her institutional mentors and her department chair, significant changes were made in her clinical activities allowing her to match those duties with her research interests.

CRTI has been critical in launching Tanya’s career and moving her along the path toward her goal of studying older adults with multiple myeloma. Taking the next step on her path, she has applied for an ASH Scholar Award based on a project looking at peripheral neuropathy as a risk factor for falls and functional decline in older adults with multiple myeloma. She is grateful to ASH for supporting CRTI and credits it with her early funding success. Tanya said, “I am not overstating it to say that CRTI changed my life and will continue to impact my career as I move forward.”

In Own Words
Dr. Wildes credits the yearlong mentoring component of CRTI with helping her maintain momentum.

“Dr. Mikhael continued to keep tabs on my progress through phone calls and emails, and he pushed me to take steps that were out of my comfort zone. He took the time to read my specific aims for my ASH Scholar Award submission, and he made suggestions for improvement. During fellowship, a senior fellow told me that ‘Nobody cares about your career but you.’ CRTI has shown me over and over again how untrue that is.”

What is CRTI?
The ASH CRTI provides an intense training experience for senior fellows and junior faculty who are interested in patient-oriented research. Twenty candidates are selected annually and spend a week with 20 faculty members in a program designed to deliver both didactic teaching in areas of clinical research (such as statistics, clinical trials design, and mentorship) and one-on-one interactions in small group workshops where individual projects are developed and refined. Attendees are matched with a CRTI mentor who serves to facilitate their career development for the subsequent year, with the intent of complementing the guidance of their local mentor.

In addition to the summer workshop, two subsequent mandatory sessions, the first at the ASH annual meeting and the second on the third Thursday in May at ASH Headquarters in Washington, DC, provide an opportunity for further interaction and mentoring throughout the year.

Important CRTI Dates
January 4: Letter of Intent Due
March 1: Application Deadline
June: Finalists Notified
August 3 - August 9: Summer Workshop
December: Follow-Up Meeting
May 15, 2014: Final Class
Recent Advances in Acute Graft-Versus-Host Disease

(Cont. from page 6)

of donor Tregs has been shown both to protect HCT recipients from lethal GVHD and to improve immune reconstitution.6 Initial clinical trials of haploidentical HCT appear to confirm these findings in humans. With Treg-enriched donor lymphocytes as the sole prophylaxis for GVHD, only two of 28 patients developed clinically significant acute GVHD, even though large numbers of conventional T cells were co-transplanted with CD34-selected donor stem cells.7 Non-hematopoietic antigen-presenting cells in the GI tract may also be attributable to the capacity of Tregs to impede the migration of conventional T cells. Functional expression of chemokine (C-C motif) receptor 5 (CCR5) is required for donor effector lymphocytes to home to the GI tract and liver and cause acute GVHD. In a phase II trial involving high-risk patients, blockade of CCR5 with maraviroc for the first 30 days after HCT resulted in a 29 percent incidence of grade B+ acute GVHD in the skin compared with an 8.8 percent incidence in the GI tract and the liver.8

Our understanding of acute GVHD of the GI tract has rapidly advanced during the last several years. Experimental systems have illuminated unexpected relationships between both the innate and adaptive arms of the GI mucosal immune system and the GI microbiota that influence the development of GVHD. Increased understanding of the complex interactions among different classes of antigen-presenting cells, including Tregs and effector T cells, and their trafficking characteristics has suggested new therapeutic strategies, now in early-phase clinical trials, that do not rely on traditional, non-specific immunosuppressants. The discovery of important predictive and prognostic biomarkers may soon provide an approach to personalization of therapy according to an individual patient’s risk of developing acute GVHD. Such advances are likely to improve outcome broadly by making allogeneic HCT safer and more effective.


2012 Honorific Award Winners

WHO: James N. George, MD, University of Oklahoma Health Sciences Center
WHAT: Wallace H. Coulter Award for Lifetime Achievement in Hematology
WHEN: Sunday, December 9, at 1:15 p.m.
WHERE: Hall B5, Building B, Level 1
WHY: Dr. George is receiving this award for his distinguished, 50-year career combining outstanding basic and clinical research investigation, extraordinary teaching and mentorship, and exceptional patient care.

INTERESTING FACT ABOUT DR. GEORGE: He never watches television.

WHO: Timothy J. Ley, MD, Washington University School of Medicine
WHAT: E. Donnall Thomas Lecture and Prize
WHEN: Monday, December 10, at 9:00 a.m.
WHERE: Hall B5, Building B, Level 1
WHY: Dr. Ley is receiving this award for his groundbreaking work that has further illuminated the molecular pathogenesis of acute myeloid leukemia.

INTERESTING FACT ABOUT DR. LEY: On their farm, he and his family have the only organic vineyard in Missouri.

WHO: Bruce R. Blazar, MD, University of Minnesota, and Carl H. June, MD, University of Pennsylvania
WHAT: Ernest Beutler Lecture and Prize
WHEN: Monday, December 10, at 1:30 p.m.
WHERE: Hall B5, Building B, Level 1
WHY: Dr. Blazar and Dr. June are receiving this award for their contributions to bone marrow transplantation and adoptive immunotherapy.

INTERESTING FACT ABOUT DR. BLAZAR: With a grant award from the NIH, Dr. Blazar was able to stay at the University of Minnesota as a faculty member after his fellowship, and he has been at that institution continuously since then.

INTERESTING FACT ABOUT DR. JUNE: He would probably be selling tied-dyed T-shirts in La Jolla and trying to learn to surf if he couldn’t work in cancer research.

WHO: Margaret A. Goodell, PhD, Baylor College of Medicine
WHAT: William Dameshek Prize
WHEN: Tuesday, December 11, at 9:30 a.m.
WHERE: Hall B5, Building B, Level 1
WHY: Dr. Goodell is receiving this award for her leadership and for her notable discoveries in stem cell biology.

INTERESTING FACT ABOUT DR. GOODELL: Dr. Goodell is the proud mother of three young daughters.

WHO: David Ginsburg, MD, University of Michigan in Ann Arbor and Howard Hughes Medical Institute, and Richard H. Aster, MD, BloodCenter of Wisconsin and Medical College of Wisconsin in Milwaukee
WHAT: Henry M. Stratton Medal
WHEN: Tuesday, December 11, at 9:30 a.m.
WHERE: Hall B5, Building B, Level 1
WHY: Dr. Ginsburg and Dr. Aster are receiving this award for their accomplishments in the fields of thrombosis and blood cell immunology, respectively.

INTERESTING FACT ABOUT DR. GINSBURG: He likes to sail and go SCUBA diving.

INTERESTING FACT ABOUT DR. ASTER: To fund his undergraduate and medical education, Dr. Aster managed a business that made and delivered sandwiches and other food items to fraternities and sororities on the University of Michigan campus.
As technology and the Web have evolved, so too have ASH’s online offerings. Now, beyond the ASH website, you can download ASH apps for your smartphone or tablet, follow ASH on Twitter (www.twitter.com/ASH_hematology), find ASH videos on YouTube (www.youtube.com/user/ASHWebmaster), and visit ASH on Facebook at www.facebook.com/AmericanSocietyofHematology.

**WHAT’S ON THE WEB**

**November**

7 Deadline for advance registration for ASH annual meeting
Atlanta, GA
www.hematology.org

27 ASH annual meeting registration cancellation deadline
Atlanta, GA
www.hematology.org

**December**

8-11 54th ASH Annual Meeting and Exposition
Atlanta, GA
www.hematology.org

14 Letter-of-intent deadline for ASH Research Training Award for Fellows
Washington, DC
www.hematology.org

**January 2013**

4 Application deadline for ASH Bridge Grant Award (first round)
Washington, DC
www.hematology.org

Letter-of-intent deadline for ASH Clinical Research Training Institute
Washington, DC
www.hematology.org

18-19 Highlights of ASH
Toronto, Canada
www.hematology.org

Highlights of ASH
San Diego, CA
www.hematology.org

25-26 Highlights of ASH
New York, NY
www.hematology.org

Highlights of ASH
Dallas, TX
www.hematology.org

**February**

1-2 Highlights of ASH
Miami, FL
www.hematology.org

Highlights of ASH
San Francisco, CA
www.hematology.org

Later this month, the complete 2012 annual meeting program will be available as a mobile app for iPhone, Android, and Blackberry smartphones, as well as iPad and Android tablet devices.

Download this exclusive app to access full text of all annual meeting abstracts, articles from Hematology 2012 (The Education Program), maps of the Georgia World Congress Center, general meeting information, and more. The app also allows users to create personalized meeting itineraries and communicate in real time with other annual meeting attendees via a messaging function. The 2012 ASH Annual Meeting mobile app includes several new features based on user feedback, and ASH continues to enhance this free, user-friendly tool.

The app will be available for download in late November in advance of the meeting. To download, search for “ASH2012” in your device’s app store. Attendees are strongly encouraged to download the app prior to their arrival at the meeting in order to enjoy the full benefits of the app and avoid delays during the download process.

For more information and a video tutorial on the 2012 ASH Annual Meeting mobile app, visit www.hematology.org/ash12app.

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