New Means to Reactivate p53 in Leukemia: A Stapled Peptide Inhibitor of MDMX and MDM2


The tumor suppressor TP53 is well recognized as one of the most commonly deregulated genes in cancer and is affected by deletions, and both loss-of-function and change-of-function mutations. Additionally, several natural inhibitors exist in the cell as endogenous inhibitors of TP53 function. These include the proteins MDMX (also known as AML17 and MDM4) and MDM2. MDM2 is an E3 ubiquitin ligase that targets TP53 for destruction while MDMX represses TP53 transcriptional activity. Current efforts to therapeutically target cells bearing altered TP53 include efforts to restore the wild-type function of TP53 or deplete, inhibit function, or induce synthetic lethality of mutant TP53. Of these strategies, the therapeutic approach that has come closest to clinical development is inhibiting the interaction of MDMX and TP53. The first such MDM2 inhibitor compounds, termed nutlin, were described in 2004. However, these compounds, which underwent trials in refractory myeloid leukemia patients, were limited by in vivo potency and poor bioavailability. Additionally, it is known that MDMX promotes MDM2 activity via direct protein-protein interactions and that efforts to inhibit MDM2-p53 interaction can be limited by MDMX activity. Thus, targeting the interactions of TP53 with both MDM2 and MDMX would be expected to have greater impact on activating wild-type TP53 function than inhibiting MDM2 alone. To this end, Aileron therapeutics, in collaboration with Dr. Ulrich Steidl’s group at Albert Einstein College of Medicine, now describe a novel therapy to inhibit TP53’s interactions with both MDMX and MDM2 using a stapled peptide known as AMLN-6924. This compound is a small molecule that consists of a peptide to inhibit the binding of TP53 to both MDM2 and MDMX and a synthetic brace (or “staple”) to lock the peptide in confirmation, increase its cell penetration, and protect the peptide from proteolytic cleavage. Aileron previously completed the first clinical trial of a stapled peptide and has now taken AMLN-6924 into phase I trials in solid tumors and lymphomas with wild-type TP53 (NCCT2284613) as well as refractory myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) with wild-type TP53 (NCCT26803972).

Upregulation of MDMX and MDM2 have been described in several cancers and result in impaired TP53 function. Dr. Steidl’s group identified that MDMX is transcriptionally upregulated in AML patients (while MDM2 is not altered in expression) compared to patients with other forms of cancer, and is specifically upregulated in leukemia-initiating cells compared to healthy hematopoietic stem cells. Then, in a series of studies, they found that use of AMLN-6924 reactivated wild-type TP53 transcriptional activity and signaling in AML cells, had (Cont. on page 2)

Diffusion

Immune Therapies in Immune Thrombocytopenia

JENNY M. DESPOTOVIC, DO

Associate Professor of Pediatrics, Baylor College of Medicine, Houston, TX

Emerging Therapies in Immune Thrombocytopenia (ITP) is an acquired bleeding disorder with a heterogeneous and incompletely understood pathophysiology. The complex interplay of abnormalities, including immune dysregulation, antiplatelet autoantibodies, defects in cellular immunity, and altered platelet production, result in often profound thrombocytopenia and variable bleeding symptoms. For decades, treatment options were limited to corticosteroids and splenectomy, followed by the plasma-derived treatments. However, as understanding of ITP disease biology improves, an expanded treatment repertoire is emerging.

Current State of ITP Treatment

Broadly, two categories of agents are available for the treatment of ITP: 1) those that rapidly and transiently interfere with the process of platelet destruction for management of acute bleeding or bleeding risk (front-line therapies), and 2) those with potential to provide a more durable improvement in the platelet count (second-line therapies). Corticosteroids, intravenous immunoglobulin (IVIG), and anti-D immune globulin remain the mainstay of front-line treatment of acute bleeding symptoms in both adults and children. Although corticosteroids remain the most commonly used ITP therapy, controversy still exists surrounding selection of agent, dosing, and duration of therapy. Several groups have investigated whether dexamethasone could be superior to prednisone in primary ITP. Dexamethasone is commonly used as a short course, at a higher dose, with faster onset of action compared to prednisone, and laboratory data suggest that dexamethasone more effectively modulates the T cell abnormalities seen in ITP. However, given the increased potency of dexamethasone, the adverse effect profile may be less favorable. A recent meta-analysis analyzed nine randomized trials comparing various steroid regimens and found that while the initial response rate may be higher in adult patients treated with dexamethasone, the durable response rates were not significantly different. The authors proposed consideration of dexamethasone instead of prednisone in adults if more rapid improvement in platelet count was desired. For treatment with prednisone, it is generally accepted that shorter courses are preferable to chronic therapy.

Choice of Second-Line Therapy

What to do next? The approach to the management of patients who fail front-line treatment or have persistent or chronic ITP has evolved dramatically since the publication of two pivotal clinical practice guidelines for the management of ITP. Both the ASH 2011 evidence-based practice guideline for ITP9 and the 2010 international consensus report on the investigation and management of primary ITP developed by an international working group10 address three classes of second-line therapies: splenectomy, rituximab, and the thrombopoietin receptor agonists (TPO-RA). While there were adequate data for the efficacy and safety of splenectomy and rituximab, both sets of guidelines were published relatively shortly after the 2008 U.S. Food and Drug Administration (FDA) approval of two TPO-RA therapies, romiplostim and eltrombopag. Due to a relative lack of data, their use was recommended only in patients who were refractory to splenectomy and other therapies. In the years since the publication of these guidelines, abundant data on the efficacy and safety of the TPO-RA have become available; as such, these treatments are being used earlier and more frequently in the disease course in both adults and children. Increasing use of rituximab and the TPO-RA agents is leading to overall reduced rates of splenectomy, especially in young children and older adults, who are considered to have the highest risk of complications after splenectomy. Future studies are likely to clarify the role of TPO-RA in earlier phases of ITP treatment.

TPO-RA Efficacy and Safety Data, and a New TPO-RA

Data on long-term use of romiplostim and eltrombopag are available in both adults and children. These studies generally show that response can be maintained and that the agents are safe for long-term use, with no additional safety signals or rates of adverse events than previously reported. Although these agents were not designed to be used with curative intent, a small number of patients have gone into extended remission after treatment with a TPO-RA, prompting additional research into the biology of the effect of TPO-RA on the bone marrow.

Avatrombopag is a newer, nonpeptide thrombopoietin receptor agonist that has been in ongoing clinical trials since its development in 2008. This drug is orally bioavailable and does not have the divalent cation interactions limiting timing of meals or potential for hepatotoxicity seen with eltrombopag therapy; it may eventually provide another alternative for patients who are good candidates for TPO-RA therapy. Data from a phase III, randomized, double-blind, placebo-controlled study of avatrombopag in adults with chronic ITP was presented at the 2017 ASH Annual Meeting.

Novel Approaches and New Therapies

Despite the increasing use of TPO-RA, many patients remain refractory to available treatments. Current research is focused on combining therapies to address multiple mechanisms of disease simultaneously. Additionally, as our understanding of the complex pathophysiology of ITP improves, novel therapies targeting alternative pathways are becoming available.

(Cont. on page 6)

Ask the Hematologist

Dr. Kendra Sweet discusses TKI cessation as a treatment option for chronic phase CML.

Mini Review

Dr. Jenny Despotovic continues coverage of emerging therapies in immune thrombocytopenia.

In Memoriam

Colleagues remember hematology trailblazer and former ASH President Dr. George Stamatoyannopoulos.

No-Data Zone

Drs. LeBlanc and Litzow discuss whether transfusions are a barrier to high-quality end-of-life care in hematology.
**Being the Change We Want to See in the World**

Having recently returned from the yearly Executive Committee Spring Retreat and Highlights of ASH meetings, I am travel-weary but nonetheless inspired by the passion and extraordinary brainpower possessed by so many in our community. From progress in acute leukemia studies in Latin America to newer immunotherapies and genome editing, the remarkable progress in the full spectrum of conditions that we collectively study and treat is undeniable. Increasingly, our basic and clinical research contributions are resonating in other areas of medicine. Yet to excel in our field today and meet the increasing demands of clinical practice, some of us have become fairly narrow in our focus — almost “sub-specialized.” My recent travels with and on behalf of our global Society have led me to think that although this may be unavoidable, we must strive to avoid myopia in our daily lives, or limit the worldview of ASH.

Advocacy is a fundamental component of the Society. As ASH President, I am proud and humbled to represent you whenever I can to deliver our message and effect change where needed, as countless individual hematologists have done over the years. They have written their congressional representatives, volunteered on committees and task forces, and otherwise made their voices heard at ASH and in the general sphere. The ASH Advocacy Leadership Institute, which just selected its newest group of hematologists, provides additional opportunities for members to become even more effective as spokespersons and champions.

ASH has made policy statements and expanded programs that may not affect us immediately, but nevertheless require action. The opioid epidemic has been an alarmingly destructive force. Even if not personally impacted by this scourge, we all appreciate the toll it is taking. The urgency to address the problem has prompted broad legislation and regulations to limit access to classes of medications that inadvertently may compromise the ability of patients with hematologic malignancies and blood disorders such as hemophilia and sickle cell disease, who have legitimate need for pain medication, to receive timely appropriate care. ASH is engaging with federal agencies and Congress on this issue to advocate for patients and providers (www.hematology.org/Advocacy/Statements/4902.aspx).

Finally, there are times when advocacy may have little to do with our specialty but instead speaks to our sensibilities and decency. My personal view as a citizen, a clinician, and a person of faith is that the current plight of children on the U.S. southern border who have been forcibly separated from their parents is inhumane and deplorable. Some of the rhetoric surrounding these actions is dangerously reminiscent of campaigns from a dark past that ultimately lead to genocide, chattel slavery, and other atrocities. Many of these past horrors occurred while those who saw no direct link to their own circumstances remained silent. I applaud organizations in communities such as the American Medical Association, Association of American Medical Colleges, American Academy of Pediatrics, and the National Medical Association for their strong statements on the tremendous harm to children, both immediate and long-term, resulting from official actions by our government. In my opinion, what we have been witnessing must not only be condemned, it must be stopped.

I appreciate my colleagues and ASH members who are engaged and outspoken regionally and locally to make a difference. I remain heartened and in fact energized by the strides we are making and by the courage ASH leadership has shown in taking on challenges with ambitious and at times audacious initiatives. Some steps may be incremental, others transformational. ASH will continue to advocate for programs and policies that will enable us to deliver on our promise to those who depend on us most — our patients and their families.

Sincerely,

Alexis A. Thompson, MD

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**New Means to Reactivate p53 in Leukemia**

(Cont. from page 1)

dose-dependent cytotoxic effects on AML cells in vitro, and reduced leukemia burden in vivo. Moreover, ARLN-6924 treatment in wild-type mice resulted in no major perturbations in hematologic parameters.

During the above preclinical studies, the investigators encountered a 20-year-old female patient with metastatic breast cancer, germline deletion of one allele of TP53, and high-risk MDS (refractory anemia with excess blasts) refractory to conventional chemotherapy. After confirming that her leukemic cells contained one copy of wild-type TP53, they were able to treat the patient with ARLN-6924 under compassionate use. Although the patient was able to be treated for 30 days before passing away from infectious complications, during treatment she experienced a rapid increase of leukemic blasts, improvement in neutropenia, and no grade 3 or 4 thrombocytopenia. Moreover, ARLN-6924 treatment in this patient reactivated TP53 transcriptional activity.

The above studies provide new hope for therapeutic activation of wild-type TP53 in leukemia and other forms of cancer. They also raise enthusiasm for further development of additional peptide inhibitors of protein-protein interactions in cancer. It is important to note, however, that the preclinical efficacy of ARLN-6924 was restricted to AML cell lines expressing wild-type TP53. Cells null for TP53 or with heterozygous change-of-function mutations in TP53 failed to respond to the compound. Thus, further efforts to develop strategies to target mutant TP53 proteins or selectively eradicated cells bearing TP53 mutations/loss remain very important.

2018 ASH Annual Meeting
Upcoming Deadlines

The 60th ASH Annual Meeting will take place December 1-4, 2018, in sunny San Diego. The meeting will provide an invaluable educational experience and the opportunity to review thousands of scientific abstracts highlighting updates in the hottest topics in hematology. Attendees can also network with top minds in the field as well as a global community of more than 25,000 hematology professionals from every subspecialty. Visit www.hematology.org/Annual-Meeting for more information.

• ASH Foundation Run/Walk registration opens – July 5, 2018, 11:00 a.m. Eastern Time
• ASH Global Capacity-Building Showcase digital poster submission deadline – July 17, 2018, 11:59 p.m. Pacific Time
• Members-only registration and housing opens – July 18, 2018, 11:00 a.m. Eastern Time
• Abstract submission deadline – August 1, 2018, 11:59 p.m. Pacific Time
• Advance registration and housing opens for nonmembers – August 8, 2018, 11:00 a.m. Eastern Time
• Call for late-breaking abstract submissions – October 18-30, 2018

Housing Fraud Alert

As registration and housing for this year’s annual meeting approach, please keep in mind that SPARGO, Inc., is the only official housing provider for the 60th ASH Annual Meeting and Exposition. Do not be misled by "pirate" housing companies and travel agencies that aggressively pursue attendees with supposedly significant discounts. ASH has no affiliation with these organizations and does not endorse their services. Deceptive tactics by these companies include:

• Informing attendees and exhibitors that the ASH hotel room block is sold out and that if you do not book with them immediately, you may not get a room
• Distributing forms or promotional materials that appear to be issued by ASH
• Broken promises to customers
• Using ASH’s name and/or logo to falsely represent themselves as being affiliated with ASH.

If you encounter one of these scenarios, contact the ASH Housing Center immediately at ashhousing@spargoinc.com. Annual meeting registration and housing information will be sent from domains ending in hematology.org or spargoinc.com. Visit www.hematology.org/Annual-Meeting/4256.aspx for more information.

Fellows and Trainees: Attend the First Ever ASH-a-Palooza at the 2018 ASH Annual Meeting

“Trainee Day,” a long tradition at ASH annual meetings, has been re-imagined as “ASH-a-Palooza.” The event takes place Friday, November 30, 2018, at 12:00 noon, at Petco Park in San Diego. Trainees can enjoy a relaxed, open learning environment in a festival-like setting. ASH-a-Palooza will feature ASH Talks, which are 20-minute presentations in the style of “TED Talks,” speed mentoring, rapid-fire learning sessions, food, and much more. For additional information and a detailed schedule, visit www.hematology.org/ASH-a-Palooza.

ASH Clinical Practice Guidelines on VTE

In collaboration with McMaster University, ASH has been working to develop 10 clinical practice guidelines on the diagnosis and treatment of venous thromboembolism (VTE). Six VTE guidelines have already been completed by the 10 expert guideline panels, which are composed of more than 100 individuals, including U.S.-based and international hematologists, clinicians from other specialties, scientists with expertise in evidence synthesis and appraisal and guideline development methodology, and patient representatives. Guidelines cover topics including diagnosis of VTE, heparin-induced thrombocytopenia, and VTE in pediatric populations. Four additional guidelines will become available in the next six to seven months. For more information in a fast and convenient format, listen to the “ASH Clinical Practice Guidelines” playlist on SoundCloud (www.soundcloud.com/ash_hematology), and subscribe to iTunes to stay up to date with future VTE guidelines opening for public comment.

ASH Global Research Award

The ASH Global Research Award is designed to support future international scientific leaders, increase hematology capacity, and nurture global collaboration. The Society’s newest award was created for trainees and early investigators practicing outside of the United States and Canada who are between completion of training and establishment of their independent careers. Letters of intent are now being accepted until August 31, 2018. For more information on eligibility and the application process, visit http://www.hematology.org/Global-Research.aspx.

Multimedia Round Up

Tune in to The Hematologist: ASH News and Reports podcast series for the latest discussions of hot topics in hematology. Make sure to subscribe to SoundCloud and iTunes to stay up to date with future installments. The June podcast features Drs. Joseph Alvarnas and Alan Rosmarin providing a thorough overview of the ASH Congressional Fellowship, with an excerpt from Dr. Catherine Zander giving us a personal take on her experience as the first ASH Congressional Fellow. The July installment consists of a thought-provoking conversation between Contributing Editor Dr. Omar Abdel-Wahab and Drs. Ulrich Steidl and Amit Verma, authors of the article covered by Dr. Abdel-Wahab in his most recent Diffusion article titled, “New Means to Reactivate p53 in Leukemia: A Stapled Peptide Inhibitor of MDMX and MDM2.” New videos are available in the “Conversations With Innovators” series. In the latest video, Dr. David Garcia of University of Washington discusses the use of direct oral anticoagulants in cancer patients who develop blood clots.

Visit www.hematology.org/thehematologist/multimedia to view and listen to the latest videos and podcasts from The Hematologist.
The Case
A 48-year-old woman with chronic-phase chronic myeloid leukemia (CP-CML) is being treated with imatinib 400 mg daily. She was initially monitored to be in a chronic phase at the age of 43 and has been on imatinib for five years. Her Sokal risk score, at diagnosis, was low. She has met the desired treatment milestones including an early molecular response (BCR-ABL transcripts <10% on the International Scale [IS]) after three months on imatinib, and she achieved a complete cytogenetic response after 12 months on imatinib. She has had persistently low BCR-ABL TKIs that can induce complete cytogenetic responses and very deep levels of molecular response in most CP-CML patients, leading to a life expectancy that rivals that of the general population.6

Despite these positive aspects of TKI therapy, there remains a negative side to the current management of CML. For some, the idea of taking an oral anti-cancer agent daily for the remainder of their lives is overwhelming. In many cases, remembering to take a daily drug can be a challenge. Furthermore, TKIs can be associated with significant toxicity. Although some potential adverse effects such as cytopenias and transaminases are common across the entire class of drugs, each TKI has a slightly different adverse effect profile. Some of the more common toxicities include fatigue, fluid retention, muscle cramps, nausea, vomiting, diarrhea, rash, and musculoskeletal pain. Various studies have looked at the impact of TKI-related adverse events and found that even low-grade adverse events can significantly impact patients’ health-related quality of life. In addition to toxicities, TKIs present a significant financial burden to both patients and the health-care system in general. The cost of TKIs is upwards of $100,000 per year in most cases, and even with substantial insurance coverage, this cost has not significantly declined.8 Some studies have identified a correlation between high patient costs and poor adherence to treatment, as patients attempt to ration their drugs in an effort to save money.9

TKI Discontinuation Trials
For the reasons mentioned above, many CML investigators began asking the question, “Can we discontinue TKIs in patients with deep levels of molecular remission?” The first study to address this question was the STIM1 trial. This study included 180 patients with CP-CML who had achieved undetectable BCR-ABL transcripts measured by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) while on imatinib therapy. All patients had been on imatinib for a minimum of three years and had maintained a deep molecular response (DMR) for a minimum of two years. Imatinib was discontinued and patients were monitored off treatment.

The Response
The development of BCR-ABL TKI revolutionized the management of CML. The U.S. Food and Drug Administration (FDA) approval of imatinib in 2001, imatinib, along with the four other FDA-approved TKIs that have followed, changed CML from one of the leading indications for allogeneic stem cell transplantation into a chronic disease that can be managed with lifelong oral therapy.1,6 Progression into the advanced phases of accelerated or blast-phase CML has become exceedingly rare. BCR-ABL TKIs can induce complete cytogenetic responses and very deep levels of molecular response in most CP-CML patients, leading to a life expectancy that rivals that of the general population.6

The Case
Is this patient a candidate for a trial of tyrosine kinase inhibitor (TKI) cessation?

The Question
What remains unknown
Notwithstanding the promising data reported from numerous TKI discontinuation trials, it remains unclear why TKI therapy can be successfully halted in a subset of the population when we know that hematopoietic stem cells are inherently resistant to TKIs. Evidence of low-level, detectable BCR-ABL transcripts is seen in many patients who remain in TFR.10 Thus, it is conceivable that after years of being off therapy, a leukemic stem cell harboring genetic features of a more advanced or resistant CML could emerge. This possibility lends credence to the recommendation for lifelong monitoring by qRT-PCR to measure levels of BCR-ABL transcripts, even in patients who have remained in TFR for many years.

Back to the Case
The woman presented in the case had a low-risk Sokal score when diagnosed with CP-CML. She was on imatinib, with evidence of resistance, for five years. Her BCR-ABL transcripts were undetectable using qRT-PCR with a sensitivity of 4.5 logs for 3.5 years. Based on this information, she met the recommended criteria for an attempt at TKI cessation. After being counseled about the need for monthly qRT-PCR monitoring during the first year of off treatment, as well as being educated about the possibility of TKI withdrawal syndrome, the patient chose to stop imatinib. Two years after TKI discontinuation, she remained on TFR with a sensitivity of 4.5 logs for 3.5 years. Based on this information, she met the criteria for TKI withdrawal syndrome and was managed with NSAIDs as needed. The patient resolved within six months. She will continue with frequent qRT-PCR monitoring, yet the available data suggest that she has a very high likelihood of remaining in a TFR for years to follow.

Rivaroxaban Use in Patients With Atrial Fibrillation on Hemodialysis

Dear Dr. Moll,

I read your analysis [November/December 2017, Volume 14, Issue 6] of the study conducted by Dr. Thomas Mavrakanas and colleagues. I would like to point out a few discrepancies regarding the use of rivaroxaban in those with severe renal impairment (dialysis). You state that rivaroxaban should be avoided in those patients, but this is not correct.

In The Journal of Clinical Pharmacology, 2017, a study showed that rivaroxaban is safe and effective in patients with end-stage renal disease (ESRD). The study, titled "Rivaroxaban Use in Patients With End-Stage Renal Disease: Results of the ENESTfreedom Study" by Rea, D., Nicolini, F.E., and Tulliez, M., demonstrated that rivaroxaban is effective in reducing the risk of stroke and systemic embolism in patients with atrial fibrillation and ESRD.

In addition, a prospective, multicenter, non-randomized, trial published in The New England Journal of Medicine in 2018, titled "Rivaroxaban Use in Patients With End-Stage Renal Disease: Results of the ENESTfreedom Study," showed that rivaroxaban is safe and effective in patients with ESRD.

In conclusion, there is strong evidence to support the use of rivaroxaban in patients with ESRD. The data from these studies demonstrate that rivaroxaban is safe and effective in reducing the risk of stroke and systemic embolism in this patient population.

Sincerely,

Kenneth Todd Moore, MS
Scientific Director, Cardiovascular Disease, Cardiovascular and Metabolism Medical Affairs, Janssen Pharmaceuticals, Raritan, NJ


Replay:

Since the Diffusion article "Use of Direct Oral Anticoagulants in Patients on Hemodialysis" was submitted in October 2017 and published in the November/December 2017 issue of The Hematologist, there have been revisions to the prescribing information (package insert) for rivaroxaban (revised October 2018). In his letter, Mr. Moore correctly points out that the current package insert discusses dosing in patients with ESRD on hemodialysis. The rivaroxaban insert states that 15 mg of rivaroxaban once daily will result in similar plasma drug activity as 15 mg once daily in patients with a creatinine clearance of 15 to 50 mL/min (in the previous phase III atrial fibrillation study); the rivaroxaban insert reads that rivaroxaban at the usual recommended dose of 5 mg twice daily or, if two of three dose-reducing criteria are met (age ≥80 years, body weight ≥60 kg, and creatinine ≥1.5 mg/dL), 2.5 mg twice daily, leads to plasma drug activity similar to the dosing in the phase III atrial fibrillation trial. These sentences open the door for clinicians to consider rivaroxaban or apixaban in patients with ESRD.

However, the dosing conclusions are based on very limited data—a single-dose pharmacokinetic/pharmacodynamic (PK/PD) study in eight patients with ESRD for rivaroxaban, and a single-dose PK/PD study in eight patients for apixaban.

Mr. Moore’s comment that a previously published study did not show significant accumulation of rivaroxaban in dialysis patients has to be taken with a grain of salt. The study quoted investigated the PK/PD of 10 mg rivaroxaban taken once daily for seven days. The authors of that study concluded that there was no drug accumulation in patients on HD, it is noteworthy that the PK/PD data of the six patients studied showed a trend toward accumulation, as evidenced by a higher mean area under the curve, higher mean peak plasma concentration, and a longer mean drug half-life. Furthermore, no detailed data or statistical analysis are provided in the publication to back up the authors’ conclusion that the data show an absence of drug accumulation. Additionally, I wonder whether the numerical higher plasma drug levels observed with the 10 mg dose studied may be more pronounced if higher doses of rivaroxaban (15 mg or 20 mg once daily) were used. Therefore, my conclusion is that the data in the literature do not allow me to deduce that there is no drug accumulation in patients with ESRD on HD who take daily rivaroxaban, particularly the higher dose of 15 mg once daily that the package insert mentions for patients with ESRD on HD. To expand on existing data, I would like to see a study of 15 mg rivaroxaban once daily in patients with ESRD on HD, comparing day 1 and day 8 PK data.

At present, in view of the sparsity of PK/PD and clinical data on the use of direct oral anticoagulants in patients with ESRD on HD, I prefer to treat these patients with warfarin if anticoagulation is needed.

Sincerely,

Stephan Moll, MD

Emerging Therapies in Immune Thrombocytopenia

Combination Treatment
Several studies have evaluated the combination of agents targeting different aspects of the disease biology, with the goal of inducing durable remission. The combination of darbepoetin and rituximab has been evaluated in multiple trials and has been shown to provide superior results to either drug as monotherapy in some patients, and the possibility to revert lymphocyte subset abnormalities commonly seen in active disease.

The addition of cyclosporine to rituximab and dexaemathasone has also been evaluated in small adult studies and has provided enduring remission in a subset of treated patients, without substantial reported toxicity.

Recombinant human TPO (rTPO) is available outside the United States and was recently evaluated in combination with dexaemathasone compared to dexaemathasone monotherapy in newly diagnosed adults. The authors report higher day-14 and six-month overall response and complete response rates in patients who received the combination therapy.

Fostamatinib
Fostamatinib is an orally bioavailable spleen tyrosine kinase (SYK) inhibitor that received FDA approval for the treatment of chronic ITP in adults in April 2018. SYK signaling is a critical step in phagocytosis of Fc receptor–bound, antibody-coated platelets, and blockade with fostamatinib has shown favorable results in two parallel phase III randomized, double-blind, placebo-controlled clinical trials in adults with persistent or chronic ITP. Forty-three percent of patients in this refractory cohort demonstrated a response to fostamatinib after failure of other treatments including rituximab, TPO-RA, and/or splenectomy, compared to 14 percent of patients on the placebo arm. Median time to response was 15 days. The safety profile has been generally favorable in adults, with gastrointestinal adverse effects and response was 15 days. The safety profile has been generally favorable in adults, with gastrointestinal adverse effects and response was 15 days. The safety profile has been generally favorable in adults, with gastrointestinal adverse effects and response was 15 days.

Summary
ITP is an extraordinarily complex and heterogeneous disease. The highly variable response rates to agents targeting different mechanisms of immune dysregulation suggest that there may be aspects of disease biology predominating. Improved understanding of ITP pathophysiology is leading to the availability of new treatment options for even the most refractory patients. Ongoing research may eventually offer insight into individual patient disease biology and lead to possible future targeted therapeutic approaches. In combination with an expanding number of available treatment options with favorable safety profiles, targeted therapy may eventually become possible in ITP, hopefully resulting in improved response rates and less toxicity.

Other Agents
Monoclonal antibodies targeting various pathways are the subject of ongoing research as potential therapeutic options for ITP, including agents that interfere with the interaction of CD154 and CD40. This is a critical step in the development of autoreactive T cell populations. The clinical development of these agents has been limited by an increased frequency of thrombosis in early clinical trials. Therapies that interfere with Fc receptor binding via different mechanisms than the recently approved fostamatinib are also in development. An additional agent targeting the FcγRIIa receptor is also being investigated. Other thrombopoietin agonists and cytoprotective agents with the potential to augment platelet production are in various stages of development.

Don’t Miss These Two Specialized Meetings Taking Place in the Coming Months
ASH Meeting on Lymphoma Biology
This four-day, CME-accredited meeting offers a platform for laboratory-based scientists, translational investigators, pharmaceutical scientists, and others interested in lymphoma science to discuss the latest advances in the field, identify current challenges, and establish the highest priorities for future investigation. The meetings taking place August 2–5, 2018, at the Westin Washington, DC, consist of didactic sessions, abstract presentations, interactive workshops, and panel discussions. To learn more or register, visit www.hematology.org/lymphoma-biology.

ASH Meeting on Hematologic Malignancies
Join us September 7–8, 2018, at the Marriott Marquis Chicago, for the 2018 ASH Meeting on Hematologic Malignancies to gain knowledge that can help you make an immediate impact in your practice. The meeting will feature top experts in the field, comprehensive clinical content, the latest clinical research, and opportunities to interact with colleagues in an intimate, small-group setting. Attendees will also have the opportunity to hear exciting updates in core malignancies including multiple myeloma, myelodysplastic syndromes, and myeloproliferative neoplasms through our “ASH News & Reports” structured presentations. Visit www.hematology.org/malignancies for additional information and to register.
Congress Begins Work on FY 2019 appropriations Process

Following the Trump Administration’s submission of its proposed fiscal year (FY) 2019 budget earlier this year, Congress has begun the process of crafting the 12 appropriations bills that fund different government agencies including the National Institutes of Health (NIH). As this issue of The Hematologist went to press, congressional appropriators had set an ambitious schedule, pledging to finish drafting of the spending bills by the end of June. This timeline could theoretically give Congress the ability to vote on and finalize all bills before the start of the next FY on October 1, 2018; however, Congress has not passed all 12 bills on time since 1996.

The appropriations process is critical to hematology. Congress allocates funding for medical research through the NIH and supports numerous public health agencies, such as the Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA). These agencies will not be able to continue or expand vital health programs without additional funding.

Thanks to the hard work of hematology advocates from ASH and the larger biomedical research community, the NIH has seen several consecutive years of significant increases in funding including a $3 billion increase in funding in the current FY, bringing the agency’s total funding level to slightly more than $37 billion. The CDC also received an increase of $1.1 billion in FY 2018, for a total funding level of approximately $8.3 billion.

ASH Action on CAR T

ASH is actively working to ensure adequate reimbursement for chimeric antigen receptor T cell (CAR-T) therapy. This innovative treatment, currently approved for certain patients with leukemia and lymphoma, is used to treat individuals who have exhausted all other treatment options, including chemotherapy, radiation, or stem cell transplantation. Because current reimbursement systems and payment rates fall short of covering the costs associated with CAR-T therapy, institutions are forced to make difficult choices on whether to provide the treatment, resulting in long waiting lists for patients to receive the therapy. ASH continues to stay engaged on this topic as the Centers for Medicare and Medicaid Services (CMS) work to create new codes and coverage policies for these therapies. The Society submitted comments on CMS’s proposed National Coverage Determination Analysis for CAR-T as well as on CAR-T-specific proposals in the Inpatient Prospective Payment System proposed rule. Additionally, ASH staff and members have participated in meetings related to coding for CAR T including a public meeting for the Healthcare Common Procedure Coding System (HCPCS) and meetings for Current Procedural Terminology (CPT) codes. It is imperative that the coding and associated billing procedures for these new and innovative treatments are appropriately defined. With more CAR-T therapies for other conditions expected to receive FDA approval in the near future, the precedent set here will influence patient access to this entire class of treatment.

Trump Administration Releases Blueprint to Lower Drug Prices

On May 11, 2018, the Trump Administration released “American Patients First: The Trump Administration Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs.” The document identified challenges in the American prescription drug market such as high list prices for drugs, and high and rising out-of-pocket costs for consumers, as well as a blueprint for addressing these challenges. The administration identified four key strategies for reform: improved competition, better negotiation, incentives for lower list prices, and lowering out-of-pocket costs. The document also included ample opportunity for feedback. To view the comments submitted by ASH on July 16, visit www.hematology.org/advocacy/testimony.aspx.

The Passing of a True Believer

George Stamatoyannopoulos, MD, DrSci (1934-2018)

Our friend and mentor, Dr. George Stamatoyannopoulos, passed away on Saturday, June 16, 2018, at the age of 84. In addition to his nuclear family, George leaves behind many friends and colleagues in the field of biomedical research into blood and its disorders. He is owed an enormous debt of gratitude that can never be fully quantified or repaid — with hundreds, perhaps thousands of scientists and clinicians who were influenced by his considerable scientific curiosity, and scientific leadership. George’s passion for promoting knowledge and science never wavered, despite bravely battling through many years of ill health.

George was born in Athens, Greece, on March 11, 1934. His childhood was shaped by the cataclysmic events that engulfed Greece between 1939 and 1949, where the Nazi occupation, famine, and ensuing civil war scattered his family. Following the war, he completed a classical education, studying science during the evenings. He entered medical school in Athens at age 17, graduating at the top of his class. George’s professional career began in 1958 when he was awarded an MD with highest honors at the University of Athens. While serving briefly on the faculty there, his early work, based on population studies, first suggested that carriers of thalassemia were protected from falciparum malaria. He also proposed the beneficial effect of fetal hemoglobin on the clinical status of patients with j-thalassemia. This work drew the attention of Dr. Arno Motulsky, a pioneer in medical genetics, who recruited him as an instructor in the department of medicine at the University of Washington in Seattle, where George remained for his entire professional career.

George was promoted through the ranks to become a professor in 1975, and founding director and chair of the medical genetics program from 1985 to 2009. He was later appointed to concurrent professorships in the departments of pathology, genetics, and genome sciences. Throughout his career he made many key advances in our understanding of the process by which hemopoietic stem cells undergo lineage specification and differentiation to form red blood cells; how the globin genes are regulated; and how this is perturbed in common forms of anemia, particularly thalassemia and sickle cell disease (SCD). Among his many honors and awards, he was the recipient of the William Dameshek Prize (1990) and the Henry M. Stratton Medal (2002), and served as president of ASH in 1992. He authored and coauthored more than a dozen transformational textbooks and more than 400 high-impact peer-reviewed scientific articles.

The academic signposts of an eminent scientists’ life do not fully convey the impact that George had on generations of young scientists and their scientific progeny. Most of the current senior scientists in this field (including we, the authors of this In Memoriam), were given the very first opportunity to present our work at what was probably George’s most important long-term legacy to hematology — the Biennial Hemoglobin Switching Conference. These meetings were the brainchild of George and Dr. Art Nienhuis (then at the National Institutes of Health [NIH]) and were established to convene scientists and clinicians to discuss the most recent findings in the burgeoning field studying the molecular genetics of the hemoglobinopathies, including
Deep vein thrombosis (DVT) and pulmonary embolism (PE) are dreaded complications of hip and knee replacement surgery. Anticoagulants reduce the risk of these events, and current guidelines support their use beyond the duration of hospital stay (10 days for knee arthroplasty, 30 days for hip surgery). However, more recently, questions have been raised about the applicability of studies performed decades ago and the lesser value placed on antiocoagulant-related surgical site bleeding.

These questions, coupled with aspirin's low cost and toxicity profile, prompted investigators to study this agent in the postoperative setting. Dr. David Anderson and colleagues reported the results of their multicenter, double-blind, randomized noninferiority clinical trial (EPICT II) comparing extended-duration rivaroxaban (10 mg daily) 9 days for knee arthroplasty, 30 days for hip arthroplasty) with aspirin (81 mg daily) following an initial period of rivaroxaban (10 mg daily) for five days for all patients. Patients who were taking long-term aspirin were allowed to continue the regimen (at a dose less than 100 mg daily), in addition to the study drug. The primary outcome measure was symptomatic venous thromboembolism (VTE) at 90 days, and the primary safety outcome was major and clinically relevant nonmajor bleeding (CRNMB).

A total of 3,424 arthroplasty patients (1,804 hip, 1,620 knee) with a mean age of 62 years and a mean hospital length-of-stay of 3.5 days were enrolled. There was no significant difference in the rate of symptomatic VTE between the aspirin group and the extended rivaroxaban group (0.64% [91/1,717] vs. 0.70% [12/1,717], respectively; difference, 0.06 percentage points; 95% CI, −0.05–0.66). The combination of major bleeding and CRNMB occurred in 1.29 percent of the aspirin group and 0.99 percent of the extended rivaroxaban group (p=0.43). There was only one death—a fatal PE that occurred in the aspirin group 17 days after completion of aspirin prophylaxis. The authors concluded that aspirin was noninferior to rivaroxaban for extended prophylaxis following elective hip or knee arthroplasty after an initial five-day course of rivaroxaban.

For decades, the evidence from clinical trials has supported the view that a minimum of 10 days of anticoagulant therapy following elective hip and knee arthroplasty is required to reduce the risk of postoperative VTE. The results of the EPICT II study seem to contradict that dogma. So, what has changed? The answer: a lot. Surgical technique, postoperative pain control, timing of mobilization, and length of hospital stay have all changed dramatically. However, as is often observed following the introduction of novel innovations, initial enthusiasm was followed by critical reappraisal, as well as a more gradual and measured approach to implementation of these advances. Most of the striking recent reports have been focussed in relatively uncommon clinical disorders such as severe combined immunodeficiency or X-linked lymphoproliferative disease. This landmark study offers an approach for more rational low-molecular-weight heparin therapy to one of the disorders in this class.

The article reports on 22 patients with β-thalassemia that were treated at two different centers. Nine had the Pβ0 genotype with very low globin gene transcription, and the other 13 had a Pβ allele in combination with a less severe allele in most cases (Pβ0). The patients were between 12 and 25 years of age and were considered inappropriate for sibling donor stem cell transplantation. The treatment was based on purification of autologous hematopoietic stem cells, virally mediated integration of a normal β-globin gene, and reinfusion into the patient after myeloablative chemotherapy. This may sound straightforward, but delivery of the reality has been somewhat more challenging.

Selection of CD34+ cells was achieved through the use of flt3 ligand and plerixafor. Most of these cells were then used for therapeutic genetic transduction, and a small portion (2×106/kg) was retained for hemopoietic rescue in the potential event of failure of hemopoietic reconstitution. A lentiviral vector was selected for therapy and was optimised to ensure high levels of transcription and ability to generate high titres. The inserted β-globin gene had an extended structure and included elements of the locus control region as well as an allelic insertion that allowed selective monitoring of the “transduced” hemoglobin. Between 7 and 11 million transduced CD34+ cells/kg were isolated following in vitro transduction.

A troublesome issue remains, the need for myeloablative conditioning prior to reinfusion of the transduced cells. Busulfan was used in all patients and drug concentrations were monitored regularly to ensure optimal dosage for the four days of therapy. Genetically modified cells were then infused after 72 hours.

Clinical results were very strong with a very respectable median follow up of 26 months. Red cell transfusion independence was achieved in three of the nine patients with a severe Pβ0 genotype, and the rest demonstrated a 73 percent reduction in transfusion requirement. For those with a less severe non-Pβ0/Pβ genotype, the results were even more striking and all but one of the 13 patients became transfusion-independent. The concentration of “transduced” hemoglobin was measured at 34 to 100 g/L with total hemoglobin levels at 82 to 137 g/L. Moreover, additional hematological features of thalassemia, namely hemolysis and dyserythropoiesis, were also largely corrected.

A striking success of the treatment was the number of CD34+ cells that were transduced with the transgene. As such, the cells that expanded after infusion represented a genuine “polyclonal” population with between 202 and 5,501 unique integration sites. Adverse effects of therapy were modest and entirely consistent with the use of the conditioning therapy, with veno-occlusive disease being observed in two patients. Clinical factors such as age, previous splenectomy, and genotype were not predictive of response, and the primary determinant was vector copy number in the therapeutic product. Indeed, as the seven patients who achieved levels of transduced hemoglobin greater than 80 g/L all had a vector copy number higher than 0.8 in the infusion, the concept of a “gene dosage-hemoglobin response” relationship is now emerging.

These results are among the most dramatic examples of therapeutic correction of a genetic disorder by gene therapy. β-thalassemia has a global prevalence of approximately 288,000, and the authors point out that manufacturing of the therapeutic product was undertaken in 18 cases in a central processing center rather than an academic unit. As such, the authors state, “our experience suggests that these procedures could be adapted for worldwide clinical use.” Thalassemia is a Greek reference to the spirit of the sea and provided the name for a disorder found so commonly around the Mediterranean region. Ancient Greeks may not have had much use for a word for gene, but it now seems inevitable that genetic therapy represents the future management of this huge health burden.

Remission: More Than Meets the Eye

Historically, for patients with acute lymphoblastic leukemia (ALL), remission has been defined by morphology (C 5% lymphoblasts in bone marrow with hematologic count recovery). Remission status after initiation of therapy has critical implications because it can affect eligibility for salvage regimens or experimental agents on clinical trials. Failure to obtain remission after the first block of chemotherapy is sometimes used to determine if a patient should undergo hematopoietic stem cell transplantation (HSCT). Morphologic complete remission (CR) rates are often used for regulatory approval of novel therapies, for determination of success or failure of new agents in early-phase trials, and for comparison of the activity of new agents or blocks of therapy across trials. Ironically however, morphologic assessment of remission is not always straightforward because lymphoblasts are histologically very similar to hematogones (normal B cell precursors), and manual enumeration can be inaccurate when blasts are not evenly distributed in the bone marrow.

Measurement of minimal residual disease (MRD) after initiation of therapy has been shown in multiple studies to be the strongest predictor of outcomes for children and adults with ALL. MRD is used for risk stratification by all major cooperative groups because intensification of therapy for patients with poor MRD response often improves outcomes. MRD can be measured by multiple techniques, including flow cytometry, polymerase chain reaction (PCR), and next-generation sequencing. These techniques are more robust than morphology and overcome many of its limitations. Despite the power of MRD, most cooperative groups continue to rely on morphology to define remission.

The Medical Research Council (MRC) recently reported inferior outcomes in patients treated on the UKALL 2003 trial who had morphologic remission at the end of induction therapy and MRD of 5 percent or greater (“high MRD”) using PCR-based MRD. Based on these results, they proposed a new definition of induction failure (i.e., failure to obtain remission) as 5 percent or greater residual blasts either by morphology or by MRD. The authors emphasized that these results need to be verified in additional trials and with different MRD techniques.

Dr. Sumit Gupta and colleagues recently published the outcomes of children with discordant measurements of remission by MRD and morphology. They compared outcomes in 9,350 children and young adults with de novo B-precursor ALL (B-ALL) and T-precursor ALL (T-ALL) treated on Children's Oncology Group (COG) trials. On these trials, morphology was performed locally, and MRD was performed centrally in one of two laboratories. By morphology, patients were clustered into three groups: M1 (<5% lymphoblasts), M2 (5%-25% lymphoblasts), or M3 (>25% lymphoblasts). Most patients were in a morphologic remission at the end of induction (M1: 91.48% patients [97.8%]; M2: 118 patients [1.3%]; M3: 84 patients [9.8%]), and overall, morphology and MRD were concordant in most patients (9,111 patients; 97.4%).

Discordance happened in both directions in that 40 patients had M2/M3 morphology and MRD less than 5 percent (“low MRD”; 19.8% of M2/M3 patients had discordant MRD), and 164 patients had M1 morphology and greater than 5 percent blasts by morphology. Discordance was more common in patients with T-ALL (97 [6.9%] of 1,493 patients) than those with B-ALL (66 [0.9%] of 7,857 patients). B-ALL patients with M2/M3 morphology and low MRD had inferior survival (5-year overall survival [OS]) compared with patients who were concordantly in remission (Table; Figure). Nevertheless, 17 (85%) of 20 patients with MRD less than 1 percent and M2/M3 were alive at last follow-up, compared with four (40%) of 10 M2/M3 patients with low MRD that was greater than 1 percent, suggesting there may be an MRD cutoff that can identify M2/M3 patients with favorable outcomes. A pooled analysis including patients from other cooperative groups may provide sufficient power to make that determination. For patients with T-ALL, the five-year OS was no different comparing M3/M5 morphology and low MRD with those who were concordantly in remission (Table 1), but only 10 patients had M2/M3 and low MRD.

Table 1. Discordant High Morphology and Low MRD Versus Concordant Morphology and MRD

<table>
<thead>
<tr>
<th>ALL Type</th>
<th>High Morphology and Low MRD</th>
<th>5-year OS</th>
<th>Concordant morphology and MRD</th>
<th>5-year OS</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-ALL M2/M3 and MRD &lt;5%</td>
<td>72.7 +/- 9.8%</td>
<td>M1 and MRD &lt;5%</td>
<td>93.8 +/- 0.3%</td>
<td>p &lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>T-ALL M2/M3 and MRD &lt;5%</td>
<td>100</td>
<td>M1 and MRD &lt;5%</td>
<td>91.9 +/- 1.3%</td>
<td>p = 0.41</td>
<td></td>
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</tbody>
</table>

Table 2. Discordant Low Morphology and High MRD Versus Concordant Morphology and MRD

<table>
<thead>
<tr>
<th>ALL Type</th>
<th>Low Morphology and High MRD</th>
<th>5-year EFS</th>
<th>Concordant morphology and MRD</th>
<th>5-year EFS</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-ALL M1 and MRD ≥5%</td>
<td>59.1 +/- 6.5%</td>
<td>M1 and MRD &lt;5%</td>
<td>87.1 +/- 0.4%</td>
<td>p &lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>T-ALL M1 and MRD ≥5%</td>
<td>80.3 +/- 7.3%</td>
<td>M1 and MRD &lt;5%</td>
<td>87.6 +/- 1.5%</td>
<td>p = 0.01</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: B-ALL, B-precursor acute lymphoblastic leukemia; EFS, event-free survival; OS, overall survival; MRD, minimal residual disease; T-ALL, T-precursor acute lymphoblastic leukemia.

Patients with B-ALL in the M1/high MRD group had significantly inferior outcomes (5-year event-free survival [EFS]) compared with patients who were concordantly in remission; however, they had superior outcomes compared with those not in remission by morphology or MRD (Table). Of note, the average MRD levels were higher in the M2/high MRD group compared with M1/high MRD patients. Patients with T-ALL in the M1/high MRD group also had inferior five-year EFS compared with patients concordantly in remission, but their outcomes were not statistically different compared to M2/high MRD patients (Table 2).

In summary, Dr. Gupta and colleagues confirmed the results from the UKALL 2003 study that suggest patients in morphologic remission but with high MRD have inferior outcomes. The authors recommend that the definition of remission be modified to incorporate flow cytometry. Some issues do arise when considering a change in the definition of remission. First, flow cytometry requires human interpretation, and MRD quantification may not be as accurate when tested outside of a few central laboratories. Second, immunotherapies, which are now used more commonly in the treatment of ALL, can alter surface immunophenotype and impact interpretation of PCR-based MRD. Third, failure to achieve remission is counted as an event in some clinical trials. Changing the definition of remission may impact the remission rate across trials. Finally, the final decision of relapse is arguably tied to the definition of remission, and changing the definition of relapse also raises many considerations. For example, historically the duration of first remission is used to decide whether a child with relapsed ALL should undergo HSCT in second remission. These minor and circumstantial caveats aside, the data from the COG and MRC provide a compelling rationale that strongly suggests it is time to change the decades-old definition of ALL remission.

New Herpes Zoster Vaccine: What the Hematologist Needs to Know


The lifetime risk of developing herpes zoster (HZ), the clinical manifestation of varicella-zoster virus (VZV) reactivation, is estimated to be 20 to 30 percent, with an incidence in the United States of about one million cases each year. The risk typically increases with age (especially older than age 50 years) and when cell-mediated immunity is diminished, as occurs with use of immunosuppressive drugs.1-3 Zoster vaccine live (Zostavax; Merck & Co., Inc., Whitehouse Station, NJ), a vaccine containing a strain of live attenuated VZV, was approved by the U.S. Food and Drug Administration (FDA) in 2006 after it was shown to reduce the incidence of HZ by 5.3 percent in a study of 38,000 adults aged 60 years and older. The vaccine also reduced the number of cases of postherpetic neuralgia (PHN), and the severity/duration of pain associated with HZ by 66.5 percent and 61.1 percent, respectively.4 In the United States, recommendations for the use of vaccines are created by the Advisory Committee on Immunization Practices (ACIP), a committee of medical and public health experts charged by the U.S. Department of Health and Human Services to develop recommendations for the prevention, detection, and control of communicable diseases in the United States.5

ACIP recommends that zoster vaccine live be given to all adults aged 60 years and older, including those with a previous episode of HZ and those not recalling having had chickenpox. In 2011, the FDA approved the vaccine’s use in individuals 50 to 59 years of age.6 On October 20, 2017, a recombinant zoster vaccine, zoster vaccine recombinant (Shingrix; GlaxoSmithKline Biologicals, Rixensart, Belgium), was approved for the prevention of HZ in adults aged 50 years and older based on a phase III clinical study that showed a sustained efficacy of more than 90 percent against HZ across all age groups during a four-year follow-up period.7,8,9 A total of 954,326 participants were included.5-7

Given how prevalent HZ is and how frequently immunosuppressive therapy is prescribed for the treatment of hematologic disorders, the present CDC/ACIP publication by Dr. Kathleen Dooling and colleagues is highly relevant for the practicing hematologist. CDC/ACIP recommend that for the prevention of HZ and related complications, zoster vaccine recombinant is preferred over zoster vaccine live. As with zoster vaccine live, the CDC/ACIP recommend the use of zoster vaccine recombinant in all persons older than 50 years, in persons taking low-dose immunosuppressive therapy (e.g., <20 mg/d prednisone or equivalent) or immunosuppressive therapy for a short period of time.10-12 Immunocompromised patients may consider avoidance of immunosuppression or who have recovered from an immunocompromising illness (Table). These ACIP recommendations are consistent with others recommending the use of herpes zoster vaccines in immunocompromised patients.6-10

How is our practice influenced by the recent recombinant HZ vaccine study findings, the vaccine’s FDA approval, and the CDC/ACIP recommendations? In patients 50 years and older in whom immunosuppressive therapy is planned, we immunize against HZ at least two to four weeks before planned treatment. This immunization is in addition to influenza vaccine, and in certain patient subgroups (those who receive rituximab therapy or to undergo splenectomy) the so-called “triple vaccine” (pneumococcal, meningococcal, and haemophilus influenzae vaccines). With any HZ vaccination, zoster vaccine recombinant is now preferred over zoster vaccine live. While zoster vaccine live is given as a single subcutaneous dose, zoster vaccine recombinant is given as two immunizations administered six months apart. The Table provides a summary of the current CDC/ACIP recommendations, with added comments on our approach in specific patient populations.


The American College of Chest Physicians guidelines suggest indefinite anticoagulation for patients with a first unprovoked proximal DVT or PE who are not at high risk for bleeding.17 This decision to anticoagulate indefinitely has to be individualized based on the overall risk of the patient’s bleeding and the benefit of anticoagulation. We discuss anticoagulant selection and individualized risk-versus-benefit analysis by providing evidence supporting indefinite anticoagulation therapy in patients with unprovoked VTE with persistent APA or more than one type of APA who have stopped anticoagulant therapy in response to a negative D-dimer result.1-16

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The Hematologist: ASH NEWS AND REPORTS

LUIS MALPICA CASTILLO, MD, AND STEPHAN MOLL, MD
Dr. Malpica Castillo and Dr. Moll indicated no relevant conflicts of interest.
Table. CDC/ACIP Recommendations for the Use of Herpes Zoster Vaccines

<table>
<thead>
<tr>
<th>1. All immunocompetent adults aged ≥50 years, including those who:</th>
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<tbody>
<tr>
<td>• Received zoster vaccine live in the past.</td>
</tr>
<tr>
<td>• Had chickenpox, or do not recall whether they had chickenpox or not.</td>
</tr>
<tr>
<td>• Have history of herpes zoster (shingles), but not an active flare at the time of vaccination.</td>
</tr>
<tr>
<td>• Have chronic medical conditions (e.g., chronic renal failure, diabetes mellitus, rheumatoid arthritis, chronic pulmonary diseases).</td>
</tr>
<tr>
<td>2. Anticipating immunosuppression or currently mildly to moderately immunosuppressed:</td>
</tr>
<tr>
<td>a. Adults aged ≥50 years, who are:</td>
</tr>
<tr>
<td>• Anticipating immunosuppression (vaccinate ideally ≥4 weeks before treatment).</td>
</tr>
<tr>
<td>• Taking low-dose immunosuppressive therapy (e.g., ≤0.25 mg/kg/day of prednisone or equivalent, or using inhaled or topical steroids, azathioprine, mycophenolate mofetil).</td>
</tr>
<tr>
<td>• Recovered from an immunocompromising illness.</td>
</tr>
<tr>
<td>b. Adults aged &lt;50 years: ACIP does not have a recommendation to administer either zoster vaccine to people younger than 50 years.</td>
</tr>
</tbody>
</table>

2. Adults aged ≥50 years, who are: |
- Anticipating immunosuppression (vaccinate ideally ≥4 weeks before treatment).
- Taking low-dose immunosuppressive therapy (e.g., ≤0.25 mg/kg/day of prednisone or equivalent, or using inhaled or topical steroids, azathioprine, mycophenolate mofetil).
- Recovered from an immunocompromising illness.

3. Currently severely immunocompromised (e.g., chemotherapy, high-dose long-term: steroids, azathioprine, mycophenolate mofetil, others); ACIP does not have a recommendation to administer either zoster vaccine in this population.

4. Other comments:
- It is not necessary to screen, either verbally or by laboratory serology, for evidence of prior varicella infection.
- This ACIP guideline applies no matter whether patient is seronegative or serosensitive for VZV.
- Zoster vaccine recombinant is preferred over ZVL (Zostavax®).
- Zoster vaccine live is preferred if a person is allergic to Shingrix®, or requires immediate vaccination and Shingrix is unavailable.

5. Studies examined the safety and immunogenicity of RV2a vaccination administered ≥5 years after ZVL; shorter intervals have not been studied. However, there are no data or theoretical concerns to indicate that RV2a would be less safe or less effective when administered at an interval of <3 years. Clinical trials indicated lower efficacy of ZVL in adults aged ≥70 years, therefore, a shorter interval may be considered based on the recipient’s age when ZVL was administered. Based on expert opinion, RV2a should not be given <2 months after receipt of ZVL.

b. Clinicians may choose to administer a vaccine off-label, if in their clinical judgment, they think the vaccine is indicated (e.g. history of chickenpox or lack of recall whether patient had chickenpox). The patient should be informed that the use is off-label, and that efficacy and safety of the vaccine have not been tested in people younger than 50.

c. Even though it is unclear whether immunocompromised individuals on active immunosuppressive therapy will be able to build an immune response after receiving RV2a vaccine, preliminary data show that it may be reasonable to consider vaccinating patients on active immunosuppressive therapy (e.g. active chemotherapy); however, the study excluded patients with B-cell hematologic malignancies (e.g. non-Hodgkin lymphoma), or on B-cell depletion agents (e.g. Rituximab).

d. Zostavax® can be used in patients aged 60 years and older if there is no contraindication for live attenuated vaccine (e.g. HIV, pregnancy). If high dose corticosteroids (≥0.25 mg/kg/day of prednisone equivalent) are given, vaccination should be deferred for at least one month after discontinuation of such therapy.

The Usual Suspects Aren’t Always the Bad Guys! Molecular MRD Comes of Age in AML

While the morphologic designation of complete remission (CR) remains a widely used benchmark in the treatment of patients with leukemia, the persistence of submicroscopic levels of disease is a strong predictor of relapse. However, despite well-defined requirements of testing for minimal residual disease (MRD) to predict outcomes in precursor lymphoid malignancies (AML, M3A), in the acute myeloid leukemia (AML) population, the field has lagged in codifying the meaning, methods, and requisite sensitivity of MRD. A recent consensus document from the European LeukemiaNet MRD Working Party focuses on the methodological requirements for minimal residual disease (MRC) and for some molecular methods, in particular, real-time quantitative polymerase chain reaction from cDNA for well-documented molecular lesions (e.g., NPM1 mutation and fusions of RUNX1-RUNX1T1, CBFβ-MYH11, and PML-RARA).

However, not all patients have a discernable aberrant immunophenotype by MFC; 46 to 100 percent of patients have an aberrant, trackable immunophenotype that is heavily dependent on the design of the MFC MRD panels. Even more limiting, the well-characterized molecular markers listed above are found in only approximately 40 percent of patients. So how can we know if we are fulling the field and providing meaningful MRD testing for all AML patients?

Next-generation sequencing (NGS) simultaneously interrogates large numbers of genes with either focused or whole coding sequence coverage as biologically indicated, thereby enabling the examination of AML in a mutational agnostic fashion. In 2015, Dr. Jeffrey Kico and colleagues introduced molecular MRD by NGS, demonstrating different patterns of mutation clearance after induction therapy in a small group of patients: 1) all variants cleared; 2) variants partially cleared, but returned at relapse; and 3) a subset of mutations cleared while the remaining persisted during CR without significant change in their variant allele frequency (VAF). The persistence of at least one leukemia-specific mutation during morphologic CR was associated with reduced event-free survival (EFS; p=0.003; hazard ratio [HR], 3.32), and reduced overall survival (OS; p=0.02; HR, 2.88).

Recently, Dr. Mojca Jongen-Lavrencic and colleagues demonstrated broad clinical relevance of molecular MRD by NGS using a widely used, commercially available platform at both diagnosis and CR on a large cohort of 482 patients. Using just a small panel of targeted genes (e.g., <25 mutations), these researchers identified at least one myeloid-associated mutation in 89.2 percent of cases at diagnosis. When samples from these patients were tested in morphologic CR (between day 1 and 4 months postinduction), 51.4 percent had molecular persistence of diagnostic mutations. As in the study by Dr. Kico and colleagues, various patterns of MRD were identified, with most cases with mutations in DTA, TET2, and ASXL1 with original mutations in DTA; however, 46% of those mutations during morphologic CR (78.7%, 5.4% and 51.6%, respectively), often as the only persistent mutation (67.7% of cases). Collectively, these mutations are referred to as DTA mutations by the authors. In some cases, the VAF of these variants was as high as 47 percent, which is consistent with a heterozygous mutation in essentially all cells. Other mutations, particularly those in the RAS pathway, were more likely to be cleared or present at low VAF (<2.5% VAF).

The distinct behavior of the DTA mutations corroborates what is known about patterns of clonal evolution in myeloid neoplasms, with age-related clonal hematopoiesis (or clonal hematopoiesis of indeterminate potential [CHIP]) presumably underlying/preceding the leukemic clone in a subset of cases of AML. In those cases, the leukemogenic mutations are subclonal to the AML clones in the aged stem cell. Hence, while the leukemia-specific variants decrease or are cleared in CR, the recovering marrow may repopulate with the CHIP stem cell, which has a clonal advantage. Not surprisingly, the most common CHIP variants, or the "usual suspects," are DTA mutations, but during the study’s 40-month average follow-up time, these usual suspects did not carry an increased risk of progression. Although the persistence of any mutation, independent of VAF, was associated with an increased four-year relapse rate (RR; p=0.003, training cohort), when DTA and non-DTA variants were separated, only the non-DTA mutations retained the significant association with relapse (p=0.001; Figure, part A), while DTA mutations did not (p=0.19; Figure, part B) unless accompanied by a non-DTA mutation (p=0.002; Figure, part C). The risks associated with persistent non-DTA mutations were confirmed in a separate validation cohort and stood up in multivariate analysis (RR, HR, 1.88; p<0.001; EFS HR, 1.64, p=0.001; OS HR, 1.64, p=0.003) without correlation to type of disease or treatment.

The authors also compared NGS with MFC in 340 patients for whom data were available. Concordant results were found in 69.1 percent of patients, with a 73.7 percent correlation in DTA+ cases and a 26.7 percent RR in NGS–/MFC+ cases. Importantly, MFC identified MRD in 12.1 percent of cases while NGS did not (NGS–/MFC–), and NGS alone identified MRD in 18.8 percent of cases (NGS+/MFC–) with similar intermediate RR (49.8% and 52.3%, respectively).

As demonstrated by this study, NGS methods for MRD assessment in AML demonstrate clear prognostic value for non-DTA mutations. The study also highlights critical tenants of clonal evolution in AML ontology, with interfering CHIP variants (the "usual suspects" or DTA mutations) that are independent of the leukemia disease burden and progression/leukemogenic variants, or non-DTA mutations, whose presence (although not levels/VAFs) predict risk of relapse. Finally, the research highlights the independent prognostic risk associated with MFC and NGS methods. Increases in the number of genes covered by the panel could increase the overall clinical applicability of this method beyond 90 percent of patients. Additional follow-up would be required to understand the long-term significance of DTA mutations in AML patients. Thus, at this time, the following conclusions can be drawn: 1) which mutation matters, 2) how much of the mutation does not appear to matter, and 3) both MFC and NGS methods are required for MRD assessment.

Improving Standard Upfront Chemotherapy in Advanced-Stage Hodgkin Lymphoma


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Another Sickle Cell Trait Myth Bites the Dust: Sickle Cell Trait Is Not Associated With Ischemic Stroke

Are Transfusions a Barrier to High-Quality End-of-Life Care in Hematology?

THOMAS W. LEBLANC, MD, MA, MHS, FAAPHM,1 AND MARK R LITZOW, MD1

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In 2017, more than $55,000 of patients died of a hematologic malignancy. That’s more than the number of deaths from breast cancer, a more common malignancy.

Today, over half of Americans who die of cancer receive end-of-life care services via hospice. While hospice is sometimes misconstrued as a place or a building, it is more fundamentally a philosophy of care as well as an insurance benefit. Hospice was first offered in the United States in 1982 through Medicare and has since expanded to private insurers and younger patients. Indeed, growing evidence demonstrates that hospice provides very high-quality care at the end of life. Most people receiving hospice care die in their homes, in peace and comfort, surrounded by loved ones. They spend less time in hospitals and receive less aggressive treatment in their last days when these treatments are unlikely to yield meaningful benefits. As such, hospice care has become the gold standard for high-quality care of the dying in the U.S.

Unfortunately, evidence suggests that patients with hematologic malignancies are significantly less likely to use hospice care services than patients with solid tumors,1 instead receiving aggressive care at the end of life, including chemotherapy in the last 14 days of life, spending time in a hospital, intensive care unit, or emergency department in their last month, sometimes even dying in the hospital.14 Furthermore, when hematologic malignancy patients do use hospice, they are more likely to do so for a very short period of time, thus missing out on many of its benefits.15

While the origins of this problem are likely multifactorial, it is often said that hematologic malignancies themselves pose unique barriers, such as the frequent need for transfusion support.4,6 This is because transfusions are used to treat symptomatic anemia from chemotherapy, anemia from chemotherapy, anemia from chemotherapy, and anemia from chemotherapy, anemia from chemotherapy, and anemia from chemotherapy. Consequently, transfusion support can be a significant burden for patients with hematologic malignancies.9,10 This raises important questions: Why do data show about the role of transfusions near the end of life? Do transfusions truly have palliative benefits?9 There is unfortunately very little evidence to guide our thinking on this topic. To date, there have been just a few small and mostly nonrandomized, non-blinded studies assessing the palliative benefits of transfusion support in patients with cancer. These studies often include patients with solid tumors and sometimes even other noncancerous diseases, and their recent common focus has been in assessing the role of red cell transfusions in alleviating symptoms like fatigue or dyspnea. Data regarding the impact of platelet transfusions are even more lacking. What little data do exist suggest at least some benefit without clear evidence of harm. For example, in one of the largest studies to date (101 patients), 78 percent of patients receiving red cell transfusions had improvement in one of their target symptoms (fatigue, breathlessness, weakness or dizziness).9

The data are a bit clearer regarding the impact of transfusion dependence on the quality of end-of-life care. In a large SEER Medicare analysis, transfusion dependence was associated with markedly less hospice use in patients with myelodysplastic syndromes.10 Similarly, in a small, retrospective, single-institution analysis, we found that transfusion dependence was associated with more in-hospital deaths and less use of hospice care.11 Furthermore, in an analysis presented at the 2017 ASH Annual Meeting, using SEER Medicare data from over 21,000 patients with acute and chronic leukemias, we noted a markedly shorter time in hospice among transfusion-dependent (TD) patients (6 days vs. 11 days for non-TD patients, p =.001), suggesting that the need for transfusion support may significantly delay hospice enrollment.12

Absent more conclusive data on the palliative benefits of transfusions, what should practicing hematologists do? Many of us have cared for patients who we feel have derived tangible and meaningful benefits from palliative transfusion support. Some patients have experienced marked amelioration of profound fatigue or dyspnea. Others seem to have lived longer or stayed home a bit longer and had better quality of life during their last days, weeks, or months. Yet without large, robust, randomized studies, we cannot prove this. However, many of us feel strongly enough about our observations that it feels unfair and inappropriate to withhold these potentially beneficial therapies so as to enable a hospice referral. As such, many of us refer patients to hospice care late, or not at all, when we know the myriad benefits of hospice care (both of us are, in fact, board certified palliative care specialists).

In order to resolve this dilemma, it is clear that more research is needed. However, we also think there’s enough preliminary evidence and precedent among current transfusion practices to warrant pragmatic research, such as testing the care models that allow transfusion support concurrently with hospice care, perhaps even in patient’s homes. We hypothesize that this would enable many of our end-stage hematologic malignancy patients to elect hospice care sooner, and thus derive its many benefits. Earlier hospice care should translate into more time at home with family, and more time to live the end of life, with better quality of life. Patients with hematologic malignancies should not have to choose between transfusions that provide them with palliative benefits, and high-quality end-of-life care through hospice.


In Memoriam

(Cont. from page 7)

In 2015, Professor George died at the age of 98, leaving behind a legacy of research and leadership that has had a profound impact on the field of hematologic malignancies. George was a pioneer in the study of thalassaemia and SCD. The name of these conferences reflects George’s conviction that if we understood how the globin genes “switch” from the fetal to the adult program, and found of 543 proteins, this would provide the key to curing thalassaemia. Everyone studying the mechanisms that regulate erythropoiesis and globin gene expression from around the world was invited to these conferences, and George kept the field focused on the central question. Like all of us, George was all too human — he argued vociferously; he was not always right, but he was eternally passionate about using his prodigious knowledge and intellect to crack this scientific puzzle.

George always made a special effort to promote the careers of the young researchers who were actually making these discoveries by inviting them to present their data to their peers, allowing them to defend the experiments and their implications. In this way, he marshaled international interest in globin gene regulation for the past 40 years. These conferences had, and still have, lectures and poster presentations that extend all day and into the night, marking some conferences as two-and-a-half day events into the early morning hours. To say that these discussions during the meetings were lively is an understatement. George’s passion for understanding globin gene regulation and developing new ways to treat the hundreds of thousands of patients with hemoglobin disorders was infectious and continued to shape the field through many fruitful stages.

George witnessed and contributed to the vastly improved diagnosis and treatment of hemoglobinopathies, and progress toward care via stem cell transplantation, gene therapy, and the realistic prospect of genome editing in the near future.

Everyone in our field would agree that such progress would not have developed as it has without George’s considerable national and international influence promoting our field in journals, societies, via pharma and biotech, and at NIH. Our gratitude for his spirit and for his passionate pursuit of exploring the molecular genetics of hematology for the good of mankind cannot be overstated. Our community will miss him enormously while we endeavour to pursue the scientific goals George established with the zeal his legacy should expect and demand.

As with many great scientists, George had wide-ranging intellectual interests, with an enduring love of history and philosophy. He was an active participant of the largest private collections in the world of early printed books including Renaissance and post-Renaissance editions of classical Greek and Byzantine authors. He also spent his spare time using genetics to trace the origins of diverse European and particularly Greek populations: a topic on which, during his later years, he became an internationally recognized expert.

George is survived by his wife, Dr. Thalia Papapannopoulos, his two sons, Alex and John, and three grandchildren. Thalia and John shared George’s life and his passion for biomedical research, and both continue to serve on the faculty at the University of Washington.

George requested to be buried in his beloved ancestral village near the Homeric town of Kyparisia in Greece.

—Doug Engel, PhD, Professor, Department of Cell & Developmental Biology, University of Michigan

—Doug Higgs, FRSA, Director, MRC Molecular Haematology Unit, MRC Weatherall Institute of Molecular Medicine, University of Oxford
Targeting a Myeloma Translocation for the First Time: The t(11;14) Journey

**STUDY TITLE:** A Phase 1/2, Multicenter, Dose-Escalation and Expansion Study of Combination Therapy With Venetoclax, Daratumumab and Dexamethasone (With and Without Bortezomib) in Subjects With Relapsed or Refractory Multiple Myeloma

**ISRCTN NUMBER:** NCT03314181 (ClinicalTrials.gov identifier)

**SPONSOR:** AbbVie

**ACCRUAL GOAL:** 90

**PARTICIPATING CENTERS:** 32 centers in the United States, Canada, Australia, and Europe

**STUDY DESIGN:** This is a relatively complex study with two primary parts. Part 1 includes patients with relapsed/refractory multiple myeloma (MM) carrying a t(11;14) translocation, as determined by fluorescent in situ hybridization. Part 2 allows entry of any relapsed/refractory MM patients. Both parts begin with a dose-escalation phase (1a, 2a) followed by an expansion phase (1b, 2b). Part 1 patients will be treated with venetoclax, daratumumab, and dexamethasone, while part 2 patients will be treated with venetoclax, daratumumab, bortezomib, and dexamethasone. Although part 2b comprises a single-arm, open-label study of venetoclax (dose defined in 2a), daratumumab (15 mg/kg intravenously), bortezomib (1.3 mg/m² subcutaneously or intravenously, cycles 1-8), and dexamethasone (20 mg for cycles 1-8 and 40 mg weekly for cycles 9-3), part 1b involves random assignment to one of two arms — either the venetoclax (dose defined in 1a), daratumumab (as above), and dexamethasone (as above) arm, or the placebo, daratumumab, and dexamethasone arm. Participants must not have been previously treated with venetoclax (or another BCL-2 inhibitor) or daratumumab (or another anti-CD38 antibody).

The primary endpoint for part 1 is objective response rate (ORR), defined as the proportion of participants with partial response (PR) or better based on IWG criteria, or number of participants with dose-limiting toxicities. For part 2, the primary endpoint is complete response (CR) or better (CR or stringent CR, based on IWG criteria), or number of participants with dose-limiting toxicities.

Secondary endpoints include progression-free survival (PFS), time to progression, duration of response, ORR, Cmax of daratumumab, Cmax of venetoclax, Tmax of venetoclax, and minimal residual disease (MRD). MRD negativity is defined as less than 10⁻⁶ tumor cells in bone marrow aspirates by next-generation sequencing at the time of suspected CR/stringent CR, and at six and 12 months post confirmation of CR/stringent CR for maintained response.

**RATIONALE:** BCL-2 inhibition has been shown to be effective in myeloma in vitro and in clinical trials. More specifically, MM cell lines with t(11;14) translocation, as well as patients with t(11;14), have been shown to be particularly sensitive to BCL-2 inhibition. However, the role of BCL-2 inhibition in patients with t(11;14) is still under investigation. In this trial, BCL-2 inhibition by venetoclax is being tested for safety and efficacy in combination with bortezomib, dexamethasone, and daratumumab, an anti-CD38 monoclonal antibody that has recently been approved as first-line treatment for MM. The effects of BCL-2 inhibition on t(11;14) myeloma are assessed separately.

**COMMENT:** MM is genetically complex. Although there are genes that are recurrently mutated more often than expected based on their length, expression level, and replication timing, for several reasons those mutations cannot be used to effectively categorize myeloma patients. First, even the most commonly mutated genes, KRAS and NRAS, are only mutated in 20% of cases, and second, even collectively, cases with mutations in those genes only account for approximately 60% of the patient population. Structural variation, on the other hand, is much more reliable as a myeloma biomarker in that it accounts for all myeloma patients. Roughly half of cases have hyperdiploid genomes with multiple copies of the odd-numbered chromosomes, while the other half carry translocations involving IgH. These translocations comprise primary events that pair IgH enhancers with five partner genes, including CCND1 on chromosome 14, CCND3 on chromosome 6, MAFET/FGFR3 on chromosome 4, CMAP on chromosome 16, and MAFF on chromosome 20, leading to upregulation of said genes and oncogenesis. Therapeutic targeting of t(11;14)–translocated cancer has been one of the biggest successes in the history of cancer treatment and precision medicine, which makes targeting translocated myeloma particularly appealing, especially t(11;14) cases, as this translocation occurs in other malignancies as well, most commonly in mantle cell lymphoma (MCL).

Myeloma patients with t(11;14) comprise approximately 15 to 20% of all cases, making t(11;14) the most common of its translocations. Notably, its frequency is even higher in cases with plasma cell leukemia (~40%). Although t(11;14) used to be considered a standard risk factor, it is increasingly thought of as an intermediate risk factor in the era of novel agents, conferring inferior outcome compared with standard-risk myeloma. By juxtaposing IgH with CCND1, the latter is overexpressed, leading to kinase activation and tumor cell proliferation.

Myeloma cases with t(11;14) are predicted to be BCL-2-dependent. BCL-2 is a member of the BCL-2 family of antiapoptotic proteins, which also includes MCL-1 and BCL-XL. MM is heterogeneous with respect to BCL-2, MCL-1, and BCL-XL dependency, with some cases being more dependent on MCL-1 over BCL-2 and vice versa. Multiple studies in human myeloma cell lines demonstrated that the presence of t(11;14) was predictive of BCL-2 dependency, making BCL-2 a potential target in this subtype of myeloma. These studies also showed that t(11;14) lines were significantly more sensitive to BCL-2 inhibition — an effect that was associated with the ratio between BCL-2 and MCL-1/BCL-XL expression. Higher MCL-1 expression weakened the effect of BCL-2 inhibition but could be circumvented with concurrent use of bortezomib, which suppresses MCL-1. Furthermore, dexamethasone was shown to act synergistically with BCL-2 inhibition through alterations in the interplay between BCL-2 and the proapoptotic bax Bim. In vitro, BCL-2 inhibition, either as monotherapy or in combination with bortezomib and dexamethasone, had superior performance in myeloma with t(11;14).

A couple of clinical trials followed. BCL-2 inhibition by venetoclax as monotherapy in patients with relapsed/refractory MM was shown to be safe and effective. Dr. Shaji Kumar and colleagues observed that almost all of the responses recorded happened in patients with t(11;14), while BCL-2/MCL-1 and BCL-2/BCL-XL expression ratios were predictive of that effect, just like in cell lines. In parallel, Dr. Philippe Moreau and colleagues tested the combination of venetoclax with bortezomib and dexamethasone in patients with relapsed/refractory MM and found a significantly higher ORR in cases with higher BCL-2 expression, but failed to observe a difference based on the presence of t(11;14). This of course could be because of the small number of cases harboring t(11;14) in that particular study, or it could be that the presence of t(11;14) is not the only strongest predictor of BCL-2 dependency. This study’s results, however, challenged the importance of BCL-2 inhibition in t(11;14) myeloma cases in the context of bortezomib/dexamethasone treatment.

This is a phase 1/2 trial, and as such it cannot answer clinically important questions regarding the superiority of treating t(11;14) myeloma patients with venetoclax. However, it is positioned to generate interesting preliminary data that will fuel the trials that will follow. Following the negative results of the study by Dr. Moreau and colleagues as far as t(11;14) status is concerned, in the context of bortezomib treatment, this trial will generate data of a preliminary comparison between venetoclax-daratumumab-dexamethasone and venetoclax-daratumumab-bortezomib-dexamethasone. At the same time, thanks to this trial’s nested randomized approach, there will be data comparing the combination of venetoclax-daratumumab-dexamethasone to placebo-daratumumab-dexamethasone, which will give us a sense of whether there is a benefit in adding venetoclax to the existent combination in the context of t(11;14) or not.

This trial will not be powered to allow a definitive answer to that question. But, as this is the first trial that recruits t(11;14) patients separately, the number of t(11;14) cases is expected to be much higher than that in previous trials. This in and of itself places this trial in a better position to address BCL-2 inhibition in t(11;14) myeloma.

Why is that important? Because t(11;14) patients are quite common and are generally predicted to have worse outcome compared to standard-risk myeloma, and even standard-risk myeloma is an incurable disease with improving, yet still quite poor prognosis. A targeted approach to therapy for patients with t(11;14) and their underlying genetic abnormalities is a promising step forward.


— Romanos Sklavenitis Pistofidis, MD, and Irene M. Ghobrial, MD

**Dr. Sklavenitis Pistofidis and Dr. Ghobrial indicated no relevant conflicts of interest.**
April 5, 2018

Dr. Nicola Gökbuget and colleagues report high rates of response, 78 percent, and improved survival with blinatumomab immunotherapy for adults with minimal residual disease-positive precursor B-cell acute lymphoblastic leukemia.

April 12, 2018

The results of this multicenter phase 2 study of the use of venetoclax for patients with chronic lymphocytic leukemia that progresses during or after treatment with ibrutinib or idelalisib reveal a high objective response rate (67%) and an estimated progression-free survival of 79 percent at 12 months, with only moderate toxicity.


The effects of Notch signaling in hematopoietic stem and progenitor cells have remained controversial. Dr. Sara Duarte and colleagues investigated genetically with the Notch transcriptional complex in hematopoiesis, demonstrating that canonical Notch signals are dispensable in primitive hematopoietic progenitors as well as across the myeloid, erythroid, and megakaryocytic lineages.

April 19, 2018

Dr. Jan Hülßdünker and colleagues reveal an unexpected role of neutrophils as antigens-presenting cells in the initiation of graft-versus-host disease.


Dr. Gerbring Berger and colleagues further elucidate the relationship between pre-existing clonal hematopoiesis of indeterminate potential and the development of therapy-related myeloid neoplasm (t-MN) following autologous stem cell transplant. They demonstrate that t-MN originates in stem cells bearing mutations that are present years before disease onset.

April 26, 2018

The investigators used an innovative genome editing approach to induce fetal hemoglobin, which may lead to therapeutic strategies for sickle cell disease and β-thalassemia.

May 3, 2018

Dr. Shuichi Takahashi and colleagues report that while topical steroids worsen skin stem cell loss in a murine model of graft-versus-host disease, ruxolitinib protects skin stem cells, restores hair growth, and promotes wound healing.

May 10, 2018

This plenary paper presents a potential mechanism of thrombosis in antiphospholipid syndrome. Using in vitro and in vivo approaches, the investigators obtain detailed insight into the role of the endothelial cell apoER2 receptor complex and downstream signaling in inducing antiphospholipid-induced thrombosis. The study also reveals novel pharmacological targets for antiphospholipid antibody-associated thrombosis.

May 17, 2018

In this plenary paper, Dr. Rafael F. Grace and colleagues provide a comprehensive overview of the clinical spectrum of pyruvate kinase deficiency (PKD). This retrospective study of 254 patients elucidates the broad range of the clinical severity of PKD and characterizes the complex genotype-phenotype relationship of this rare disease, providing important entry points for further study.

May 24, 2018

It is still a mystery why patients with chronic granulomatous disease (CGD) have autoimmune and autoinflammatory symptoms. In a compelling study, the investigators provide data to explain the molecular basis for the exuberant inflammation seen in patients with CGD, demonstrating that these patients cannot handle apoptotic neutrophils properly because their macrophages lack the capacity to sufficiently degrade these apoptotic cells.


This study adds to the broad general concept that blood clotting proteases possess remarkable biologic activities independent of their influence on coagulation. It presents the discovery that coagulation factor Vlla exerts physiologically relevant protective effects in endothelial cells and whole-organism inflammatory responses by initiating cell signaling that is anti-inflammatory via at least two receptors, endothelial protein C receptor (EPCR) and protease-activated receptor 1 (PAR1).

Featured content from Blood Advances, Volume 2, Issue 13
Trispecific Killer Engager CD16xIL15xCD33 Potently Induces NK Cell Activation and Cytotoxicity Against Neoplastic Mast Cells

In this article, the authors indicate the normal nature of natural killer (NK) cell natural cytotoxicity and antibody-dependent cellular cytotoxicity of patients with systemic mastocytosis. Additionally, trispecific killer engagers (161533 TriKE) target NK cells from normal donors and systemic mastocytosis patients to kill mast cells. Systemic mastocytosis (SM) invariably involves the bone marrow (BM) and is categorized into indolent, smoldering, and advanced forms, which have poor prognostics and include aggressive SM, SM with an associated hematologic neoplasm (AHN), and mast cell leukemia. Given the lack of established standard therapy for advanced systemic mastocytosis (adSM), novel treatments are needed. We reported that neoplastic mast cells (MCs) were persistent after haploidentical natural killer (NK) cell therapy, and that NK cells poorly targeted ROSA26-hIL15 and HMC-1.1 neoplastic MC lines. Our group has described a trispecific killer engager (TriKE) that amplifies NK cell-mediated killing of CD33 myeloid targets by splicing together a single-chain variable fragment (scFv) against CD16, an scFv against CD33, and interleukin-15 (IL-15) inserted between the 2 as a linker (termed 161533 TriKE). The goal of this study was to demonstrate that the 161533 TriKE can trigger NK cell activation against neoplastic MCs expressing CD33 as a promising therapeutic strategy in SM.

Unusual Spindle Cell Lesion Involving Bone Marrow

GIRISH VENKATARAMAN, MD,1 AND JOHN KENNEDY SYDNEY SIR PHILIP, MD2
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A 65-year-old man presented with syncope. Imaging showed mild hepatosplenomegaly. No skin lesions were observed. Laboratory evaluation detected pancytopenia with a complete blood count showing the following:

- White blood cell count: 4.3 × 10³/µL
- Hemoglobin: 8.1 g/dL
- Platelet count: 35 × 10³/µL

These results prompted a subsequent bone marrow biopsy. Peripheral blood smear showed rare abnormal circulating cells (Figure 1). Bone marrow core biopsy showed clusters of spindle cells adjacent to bony trabeculae (Figure 2) that were positive for CD117 (Figure 3). Scattered teardrop cells were also noted. Molecular testing by next-generation sequencing (NGS) detected diagnostic mutations.

What is the diagnosis?
A. Metastatic spindle cell melanoma
B. Primary myelofibrosis
C. Systemic mastocytosis
D. Langerhans cell histiocytosis

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