Universal Precautions Help Decrease Rate of Exercise-Related Death in Patient With Sickle Cell Trait


Exercise-related death has previously been associated with sickle cell trait. Evidence for this association was based initially on case reports from military recruits. Subsequently, a landmark population-based study conducted by the U.S. armed forces and published in 1987 indicated that during basic training, recruits with sickle cell trait had a relative risk of death of 27, when compared to those without sickle cell trait. Recently, multiple Division I football players with sickle cell trait have sustained injuries or died while practicing. On behalf of the surviving families, multiple lawsuits were filed against the National Collegiate Athletic Association (NCAA), the NCAA implemented a mandatory edict that all student athletes in Divisions I, II, and III receive sickle cell trait testing. Despite the public health premise that screening for a genetic disease should be coupled with genetic counseling for informed reproductive decision, the NCAA’s decree of mandatory screening was not accompanied by compulsory genetic counseling of the athlete, their significant other, or both. However, the NCAA policy did include a provision for the athlete to opt out of the sickle cell trait screening provided that the athlete sign a waiver of liability against the NCAA and their institution.

Noting concerns about the NCAA’s policy requiring mandatory screening for sickle cell trait of all incoming student athletes, ASH convened a 2011 workshop of experts to evaluate the evidence for the association between sickle cell trait and death during rigorous exercise. The experts reviewed all of the available literature, including evidence from branches of the U.S. armed forces that instituted universal precautions to prevent heat-induced and exercise-induced injury and death and noted a significant decline in death for both black recruits and white recruits during basic training. Ultimately, the experts determined that current scientific evidence did not justify this requirement and was not consistent with good medical practice or established principles of public health ethics. Based on the expert review and discussion, ASH released a Statement on Screening for Sickle Cell Trait and Athletic Participation (www.hematology.org/Advocacy/Statements/2650.aspx) in 2012, which specifically, recommends the implementation of universal interventions to reduce exertion-related injuries and deaths because this approach can be effective for all athletes, irrespective of their sickle cell status. The policy statement notes that the NCAA’s screening policy has unintended consequences, including, but not limited to harming the student athlete and the larger community of individuals with sickle cell trait if other risk factors are not considered and if the application of their mandate resulted in stigmatization and possible discrimination. Finally, the ASH policy statement calls for more biomedical and population-based research on sickle cell trait and adverse health outcomes. The provisions in the ASH policy statement are available on the ASH website (www.hematology.org/Advocacy/Statements/2650.aspx).

We now have the strongest possible evidence that implementing universal precautions to prevent dehydration and heat-induced and exercise-induced illness, as outlined by the U.S. armed forces,1 will not result in an increased rate of death in individuals with sickle cell trait, when compared to those without sickle cell trait. In a large retrospective analysis of U.S. armed service recruits, Dr. D. Alan Nelson and colleagues employed Cox proportional-hazards models to test whether death and exertional rhabdomyolysis occurred more frequently in those with sickle cell trait versus those without. Sickle cell trait status was determined in 47,944 black soldiers, of whom 7.4 percent had sickle cell trait. In soldiers with sickle cell trait (vs. those without), the percentage of all cause of death was similar (0.2%), with no statistical difference in the hazard ratio of death observed (hazard ratio, 0.99; 95% confidence interval [CI], 0.46 to 2.13; p=0.97). However, for exertional rhabdomyolysis there was an absolute difference in those with sickle cell trait (vs. those without) of 0.4 percent (1.2% vs. 0.8%), with an increase in the corresponding hazard ratio (1.54 [95% CI, 1.12 to 2.12]; p=0.008).

Dr. Nelson and colleagues, through a large cohort study, provide the foundation for implementing the U.S. armed forces universal precautions during extreme physical training for all high school and college athletes regardless of their sickle cell status. This strategy could reduce the number of exercise-related deaths for all participants and possibly decrease the prevalence of death from Division I football and heat- and exercise-induced illness. For athletes participating in extreme physical training regimens, applying universal precautions will decrease the likelihood of preventable deaths and illness. The emphasis, however, should be placed on educating physical trainers for high school and college sports programs to implement key aspects of the U.S. armed forces’ universal precautions strategies. Potentially, certification and documentation of adherence to these universal precautions will prevent unnecessary death and acute illness for countless athletes who push themselves to become the best at their sport. However, the universal prevention strategies are not without limitations including costs, logistical and personnel time for initiating and following up on the recommendations. Future research will be needed to identify the minimal set of universal prevention requirements that can be applied to not only the multi-billion dollar industry of Division I football programs, but also to college and high school sports programs with meager resources.


ASH Honors the Life and Work of Dr. David Grimwade With Exemplary Service Award

NOTE: Dr. Grimwade’s colleagues are compiling a book of remembrances for his family. Those interested in contributing may send them to remembering.david.grimwade@gmail.com.

In early October 2016, ASH announced that the Exemplary Service Award would be presented to Dr. David Grimwade, who passed away on October 16. Dr. Grimwade served as a Professor of Molecular Hematology at King’s College London, and was a member of the Department of Medical and Molecular Genetics at Guy’s King’s and St. Thomas’ School of Medicine. In addition to Dr. Grimwade’s expertise in the molecular characterization of acute promyelocytic leukemia (APL), he contributed a wealth of knowledge to the identification of prognostic factors in acute myeloid leukemia (AML) and approaches for the detection of minimal residual disease.

The award was established in 1998 in recognition of ASH members whose years of service have significantly advanced the Society’s interests. Dr. Grimwade, thanks to his deep commitment and contributions to ASH training programs, specifically the International Consortium on Acute Leukemia (ICAL) and the Translational Research Training in Hematology (TRTH), was selected for the honor just prior to his passing.

ICAL is an international network that seeks to improve the care of patients with acute leukemia. The program convenes clinical investigators from three continents in the spirit of international clinical and laboratory collaboration. Since 2007, Dr. Grimwade devoted his time and energy to sharing his expertise with his Latin American colleagues through ICAL, and in 2013 he was selected by the group to chair the Laboratory and Diagnostic Activities Subcommittee. His exemplary leadership helped guide numerous laboratory personnel in ICAL member countries to reinforce their technical and diagnostic capabilities, ultimately improving the diagnosis and treatment of acute leukemia. Dr. Grimwade was also pivotal in working with his ICAL colleagues on a chemotheraphy-free protocol for APL.

TRTH is a joint effort by the European Hematology Association and ASH that provides junior researchers with a unique, year-long training and mentoring experience to help strengthen their careers in hematologic translational research. As a TRTH faculty member, and ultimately a co-director for 2016, Dr. Grimwade mentored numerous trainees and junior faculty, who were impressed not only with his dedication and extensive knowledge and experience, but also his sense of humor and easygoing style.

[Cont. on page 13]
President’s Column

A High Note for Grand Goals

The weeks leading up to the ASH annual meeting are very busy and exciting for many of us. Whether you are presenting this year, enjoying the meeting as an attendee, or keeping an eye on all of the developing breakthroughs from home, there is a great deal to be inspired by and look forward to in San Diego this year. 2016 will be a year for a record number of abstracts, more Education and Scientific Program sessions, new joint sessions and spotlight topics, and other special events and features. (Visit www.hematology.org/AnnualMeeting for additional worthwhile offerings.) On a personal note, I am also privileged to pass the gavel over to Dr. Ken Anderson, who will lead ASH forward in 2017. As the year comes to a close, I would like to reflect on the important initiatives on the horizon that you as ASH members have helped bring to fruition in 2016.

It’s been a productive year for ASH in developing and launching the Sickle Cell Disease Coalition along with 20 other organizations, who are issuing a call to action to amplify the voice of the sickle cell disease (SCD) community. The goals of ASH and its partners over the coming years are large-scale. However, there is room for many of us to get involved in this important initiative. Priorities in the coming years include expanding newborn screening and early prevention programs globally, developing new guidelines and educational strategies to improve the care of individuals with SCD, and investing resources in research and clinical trials to accelerate the pace of discovery. We were pleased to announce the launch in September of the SCD Coalition website (www.scdcoalition.org). This new feature is the home for the campaign and offers numerous useful resources for providers. The website also highlights the “2016 State of Sickle Cell Disease”—a comprehensive summary of the current state of research, access to care, and global issues that was created by ASH and endorsed by dozens of groups. It has been amazing to watch the SCD Coalition come together over the last several months, and ASH and the entire SCD community are just getting started. Please stay tuned for more as the progress of the coalition unfolds.

In an earlier President’s Column, I shared some of my thoughts about the National Cancer Moonshot as well as the pivotal role of precision medicine in the next wave of discovery in conquering hematologic diseases. This summer, ASH announced a collaboration with the Leukemia & Lymphoma Society (LLS) to educate caregivers about the importance of clinical trials and of precision testing in AML. The scope of the collaboration has now taken a giant step with the announcement of the precision-medicine-driven Beat AML Master Trial, which will take place at multiple academic research institutions. The trial’s goals are to test a number of investigational drugs in development, with the hope of speeding up approval and increasing effectiveness of treatments for patients diagnosed with AML. ASH will provide ongoing, collaborative support in spreading the word about this important trial to hematologists and other health-care providers. Visit the ASH website or www.aml.org/beat-aml to learn more.

Lastly, ASH ends 2016 on yet another high note with the launch of a new journal, Blood Advances, just prior to the 2016 ASH Annual Meeting. This new peer-reviewed, online only, open access journal will expand the ASH family of publications, which deliver the best in cutting edge research, original observations and commentaries, point-counterpoint articles, and more. The journal will publish its first content on November 15, 2016, and will publish its first complete issue on November 29, 2016. If you are joining us in San Diego, you will have a chance to browse a special printed edition of the inaugural issue, with subsequent issues available online and via the journal app. We are also proud to have Dr. Robert Negrin from Stanford University serving as the journal’s first Editor-In-Chief. The vision of ASH and of Dr. Negrin is to provide novel approaches for presenting original content, particularly those articles best suited to the electronic format. They will include enhanced graphics, video, audio, visual abstracts, and tools for active interaction and discussion between readers and authors. Keeping pace with rapid breakthroughs and discovery is no simple feat, and it is the goal of Blood Advances to deliver cutting-edge information as rapidly as possible.

It has been an honor to serve as President of ASH this year, to work with the exceptional ASH staff, and to learn from and get to know many of the extraordinary members. I am astounded by and proud of our Society, which is really just a reflection of the talented, smart, caring, and dedicated members and staff that comprise it.

Charles S. Abrams, MD
58th ASH Annual Meeting Abstracts Available November 3

The complete ASH annual meeting schedule and program will be available to the public on the ASH website on November 3 after 9:00 a.m. Eastern Time. Read manuscripts from the education and scientific programs, as well as oral and poster sessions, general sessions, special-interest sessions, and more. Visit www.hematology.org/Annual-Meeting to browse the entire schedule by day, program, speaker, or keyword.

ASH Elects New Leadership for 2017

**VICE PRESIDENT:**
Roy L. Silverstein, MD, FACP
Professor and Chairman, Department of Medicine, Medical College of Wisconsin; Senior Investigator, Blood Research Institute, BloodCenter of Wisconsin; Associate Director, Medical College of Wisconsin Cancer Center

Dr. Silverstein will serve a one-year term as vice president followed by successive terms as president-elect and president.

**SECRETARY:**
Robert A. Brodsky, MD
Professor of Medicine and Oncology, Director, Division of Hematology, Johns Hopkins School of Medicine, Director, Hematology Fellowship Program, Johns Hopkins School of Medicine

Dr. Brodsky will serve a four-year term as secretary.

**COUNCILLOR:**
Cynthia E. Dunbar, MD
Section Head and Senior Investigator (tenured), Hematology Branch, Division of Intramural Research, National Heart, Lung and Blood Institute, National Institutes of Health

Dr. Dunbar will serve a four-year term as councillor.

**COUNCILLOR:**
John C. Byrd, MD, FACP
Director, Division of Hematology and Distinguished University Professor of Medicine, Pharmaceutics, and Veterinary Bioscience (with tenure), The Ohio State University (OSU), Member and Co-leader, Leukemia Research Program, OSU Comprehensive Cancer Center

Dr. Byrd will serve a four-year term as councillor.

The Hematologist: ASH News and Reports Podcasts

Make sure to subscribe to SoundCloud and iTunes to stay up to date with new podcast installments. The Hematologist: ASH News and Reports provides a series of podcasts covering the latest clinical topics and discoveries in hematology, as well as podcasts that promote and discuss ASH meetings, awards, and all important Society news. Listen to these podcasts via www.soundcloud.com/ash_hematology or follow us on iTunes.

The Hematologist Seeks Its Next Editor-in-Chief

ASH is in the initial stage of the selection process for the next Editor-in-Chief of The Hematologist for the term 2018 to 2020. Candidates with an MD, MD/PhD, or equivalent medical degree should have a broad and comprehensive knowledge of basic research and clinical investigation in hematology as well as an appreciation of its subspecialty areas; a distinguished research and publications record; high standing among peers; and demonstrated writing, reviewing, and editing skills. To nominate a peer by the deadline of February 1, 2017, ASH members should submit the names of potential candidates, along with a brief, informal endorsement and a description of the candidate’s editorial experience. Nominations can be submitted via email to jlllorens@hematology.org or mailed to

The Hematologist: ASH News and Reports
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Ask the Hematologists

NANCY M. DUNBAR, MD,1 AND BETH H. SHAZ, MD2

1. Medical Director, Blood Bank, Dartmouth-Hitchcock Medical Center, Assistant Professor of Pathology and of Medicine, Geisel School of Medicine, Lebanon, NH
2. Chief Medical and Scientific Officer, New York Blood Center; Adjunct Assistant Professor, Department of Pathology and Cell Biology, Columbia University, New York, NY

The Question

What are the indications for therapeutic plasma exchange (TPE) in the setting of thrombotic microangiopathy (TMA)?

Case Presentation

A 62-year-old woman presents with a several-day history of progressive fatigue and shortness of breath. Initial laboratory results demonstrate anemia (hemoglobin, 6.6 g/dL), and severe thrombocytopenia (platelets, 8 × 10^9/L). The peripheral smear review shows schistocytes representing 8.6 percent of erythrocytes counted on manual differential. Apheresis medicine is consulted for initiation of TPE for probable diagnosis of thrombotic thrombocytopenic purpura (TTP).

Our Response

Thrombotic Microangiopathies

TMA is a diverse group of inherited and acquired disorders that have multiple etiologies resulting in a similar clinical presentation of microangiopathic hemolytic anemia (MAHA, defined as hemolytic anemia with RBC fragmentation) and thrombocytopenia. TMA has multiple mechanisms, including inherited or acquired deficiency of ADAMTS-13 (TTP), and hemolytic uremic syndrome (HUS) that is Shiga toxin-mediated (previously termed "typical HUS"), complement-mediated (inherited or acquired complement defects; previously termed "atypical HUS"), drug-associated, transplant-associated, and coagulation-mediated.1 Identifying the cause of the TMA is important because appropriate treatment varies.1

Other disorders may present with MAHA and thrombocytopenia, including, but not limited to, autoimmunodysremic disorders (systemic lupus erythematosus [SLE] and antiphospholipid antibody syndrome), systemic infections, systemic malignancy, malignant hypertension, and, in the setting of pregnancy, pre-eclampsia and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count).2 Clinical history and additional laboratory testing can help narrow the differential diagnosis.1

Guidelines for the Use of Therapeutic Plasma Exchange

The American Society for Apheresis (ASFA) regularly publishes guidelines outlining evidence-based recommendations for the use of therapeutic apheresis.3 These guidelines are updated every three years by ASFA writing committee members using a uniform approach to review existing literature and assign category recommendations based on current evidence (category I, first-line therapy; category II, second-line therapy; category III, role of apheresis is unknown; and category IV, not indicated). The strength of the recommendation reflects the methodological quality of current evidence using the GRADE system.4 Each disease or condition in summarized in a single-page fact sheet which includes the recommendation for apheresis for each indication (i.e., specific situation encountered in the disease) and apheresis modality (i.e., TPE vs. immunoadsorption), along with a comprehensive and succinct summary of the disease, current management, and rationale for therapeutic apheresis.

Disease names, category recommendations, and indications for some diseases have been modified with each guideline update to reflect current recommendations based on improved understanding of disease mechanisms and emergence of new evidence. Significant changes in the 2016 update include 14 new fact sheets. There are currently 18 category I indications for TPE, including two new fact sheets in the 2016 edition (N-methyl-D-aspartate receptor antibody encephalitis* and Paroxysmal nocturnal hemoglobinuria). In addition, category I indications for TMA (previously referred to as HUS) have been modified. Changes to TMA-specific fact sheets include a new fact sheet for coagulation-mediated TMA (?THBD mutation, category III); an update to complement mediated TMA due to Factor H autoantibodies; and previously termed "atypical HUS"), drug-associated, transplant-associated, and coagulation-mediated.1 Identifying the cause of the TMA is important because appropriate treatment varies.1

Category I Indications for TPE in TMA

In the 2016 guidelines, there are three category I indications for TPE in the setting of TMA (TPP, complement-mediated TMA due to Factor H autoantibodies, and drug-associated TMA due to ticlopidine; Table 1). These disorders share the feature of antibody production resulting in endothelial damage (TTP and Factor H autoantibodies) and/or deficiency (typically <10%) of ADAMTS-13 (TTP and ticlopidine-associated TMA) or complement regulators (Factor H autoantibodies). TPE in these disorders removes the autoantibody and replaces ADAMTS-13 protein or complement regulators by using plasma as the replacement fluid.

These disorders are in contrast to those that have different mechanisms that may result in similar clinical presentations but for which TPE is not recommended owing to evidence that it is ineffective or harmful (category IV). These include ganciclovir or quinoline-associated TMA or Shiga toxin-mediated TMA in the absence of severe neurological symptoms. Ganciclovir-associated TMA is thought to be caused by drug-associated damage to the renal microvasculature, and existing evidence does not demonstrate any survival benefit when TPE is used for this disorder.5 Although quinoline-associated TMA seems to be antibody mediated (quinine-dependent antibodies target platelet glycoproteins and other cells), ADAMTS-13 levels

Table 1. Category and Grade Recommendations for TPE Category I Indications

<table>
<thead>
<tr>
<th>Disease Name</th>
<th>Indication</th>
<th>Category</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute inflammatory demyelinating polyradiculoneuropathy/Guillain-Barre syndrome</td>
<td>Primary</td>
<td>I</td>
<td>1A</td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>TPE-high volume</td>
<td>I</td>
<td>1A</td>
</tr>
<tr>
<td>ANCA-associated rapidly progressive glomerulonephritis (granulomatosis with polyclonal ANCA)</td>
<td>Dialysis dependence</td>
<td>I</td>
<td>1A</td>
</tr>
<tr>
<td>ANCA-associated slowly progressive glomerulonephritis (granulomatosis with monoclonal ANCA)</td>
<td>Dialysis dependence</td>
<td>I</td>
<td>1A</td>
</tr>
<tr>
<td>Anti-glomerular basement membrane disease (Goodpasture’s syndrome)</td>
<td>DAH</td>
<td>I</td>
<td>1C</td>
</tr>
<tr>
<td>Anti-glomerular basement membrane disease (Goodpasture’s syndrome)</td>
<td>Dialysis independence</td>
<td>I</td>
<td>1B</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyradiculoneuropathy</td>
<td></td>
<td>I</td>
<td>1B</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>Recurrent in transplanted kidney</td>
<td>I</td>
<td>1B</td>
</tr>
<tr>
<td>Hyperviscosity in monoclonal gammapathies</td>
<td>Symptomatic</td>
<td>I</td>
<td>1B</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Moderate-severe</td>
<td>I</td>
<td>1B</td>
</tr>
<tr>
<td>N-methyl-D-aspartate receptor antibody encephalitis*</td>
<td></td>
<td>I</td>
<td>1C</td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria/chronic acquired demyelinating polyneuropathies</td>
<td>IgG/IgA</td>
<td>I</td>
<td>1B</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy associated with natalizumab*</td>
<td></td>
<td>I</td>
<td>1C</td>
</tr>
<tr>
<td>Renal transplantation, ABO compatible</td>
<td>Antibody mediated rejection</td>
<td>I</td>
<td>1B</td>
</tr>
<tr>
<td>Renal transplantation, ABO incompatible</td>
<td>Desensitization, LD</td>
<td>I</td>
<td>1B</td>
</tr>
<tr>
<td>Thrombotic microangiopathy, complement mediated**</td>
<td>Factor H autoantibodies</td>
<td>I</td>
<td>1C</td>
</tr>
<tr>
<td>Thrombotic microangiopathy, drug associated**</td>
<td>Ticlopidine</td>
<td>I</td>
<td>1B</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura**</td>
<td></td>
<td>I</td>
<td>1A</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>Fulminant</td>
<td>I</td>
<td>1C</td>
</tr>
</tbody>
</table>

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; DAH, diffuse alveolar hemorrhage; LD, living donor; TPE, therapeutic plasma exchange.

*TMA-specific fact sheets

The evolution of guidelines for the use of TPE in the setting of TMA (previously termed TTP/HUS) is summarized in Table 2.3 While TTP has remained a standalone fact sheet with a category I recommendation for TPE in the last four publications, other TMAPs that were initially combined in a single fact sheet in the 2007 edition are now described in five separate fact sheets in the 2016 edition. Additional changes to TMA-specific fact sheets include a new fact sheet for coagulation-mediated TMA (THBD mutation, category III); an update to complement mediated TMA recommendations (complement gene mutations changed from category II to III; MCP mutations changed from category IV to III); and expansion of Shiga toxin-mediated TMA (previously referred to as HUS, infection-associated, Shiga toxin-associated; category IV) indications to include severe neurological symptoms (category III) and absence of severe neurological symptoms (category IV). A new fact sheet for HELLP syndrome, a mimicker of TTP in pregnant women, has also been added (category III).1

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are normal, and TPE is relatively ineffective at antibody removal. The mechanism for Shiga toxin-mediated TMA involves damage to the vascular endothelium and activation of the alternative complement pathway. Current evidence shows no benefit of TPE in patients with Shiga toxin-mediated TMA except perhaps in those with severe neurologic symptoms (category III).10-11

**Our Clinical Case**

In our case, laboratory evidence of MAHA and thrombocytopenia in the absence of any other causes of TMA based on clinical history and laboratory testing was sufficient for prompt initiation of TPE for suspected TTP.3 Prior to TPE initiation, an ADAMTS-13 level was obtained, and intravenous steroids were started. After urgent venous catheter placement, we performed a 1.5-volume TPE using plasma as the replacement fluid. The patient was without any signs of renal or neurologic involvement at the time. However, by the next day, she was noted to be febrile overnight and having word-finding difficulties that progressed to inability to speak throughout the course of the second hospital day. This prompted us to escalate the treatment to twice-daily TPE using cryo-poor plasma. 4

The platelet count increased to 14 × 10^9/L by hospital day 3, and her mental status returned to baseline. We continued to perform daily 1.5-volume TPE. ADAMTS-13 levels returned on hospital day 4 at less than 5 percent, with an increase in inhibitor titer to 2.8. Due to her refractory disease, rituximab was added to her treatment regimen on hospital day 12.5 Platelet counts began to slowly increase on hospital day 13, and she was transitioned to daily 1.5-volume TPE. Her platelet counts are currently recovering, but remain lower than 150 × 10^9/L, along with normalization of the LDH level and improvement in her renal function. She still is receiving daily TPE on hospital day 20.

**Conclusion**

A diverse group of disorders can present with TMA. In the case of TTP, prompt initiation of TPE can be lifesaving. However, treatments vary depending on the mechanism causing the TMA, and TPE is not effective for all disorders. Recommendations for the use of TPE in TMA and other diseases are available in the ASFA guidelines and are updated every three years to reflect changes in understanding of disease mechanisms and review of existing evidence supporting the use of TPE for TMA indications.

Drs. Dunbar and Shaz indicated no relevant conflicts of interest.

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### Table 2: Defining and Categorizing TMAs Over Time

<table>
<thead>
<tr>
<th>2007 Indication</th>
<th>Category</th>
<th>2010 Indication</th>
<th>Category</th>
<th>2013 Indication</th>
<th>Category</th>
<th>2016 Indication</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTP</td>
<td>I</td>
<td>TTP</td>
<td>I</td>
<td>TTP</td>
<td>I</td>
<td>TTP</td>
<td>I</td>
</tr>
<tr>
<td>HUS; TMA; TAM</td>
<td>HUS</td>
<td>HUS, atypical</td>
<td>HUS, atypical</td>
<td>HUS, atypical</td>
<td>TAM, coagulation-mediated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic HUS</td>
<td>III</td>
<td>Atypical HUS due to complement factor gene mutations</td>
<td>III</td>
<td>Complement gene mutations</td>
<td>III</td>
<td>THBD mutation</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>III</td>
<td>Atypical HUS due to autoantibody to Factor H</td>
<td>I</td>
<td>Factor H antibodies</td>
<td>III</td>
<td>TAM, complement-mediated</td>
<td></td>
</tr>
<tr>
<td>TAM</td>
<td>III</td>
<td>Diarrhea-associated HUS or typical HUS</td>
<td>IV</td>
<td>MCP mutations</td>
<td>IV</td>
<td>Complement factor gene mutations</td>
<td></td>
</tr>
<tr>
<td>Diarrhea-associated pediatric</td>
<td>IV</td>
<td>TMA, drug-associated</td>
<td>HUS, infection-associated</td>
<td>Factor H autoantibodies</td>
<td>I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticlopidine/Clopidogrel</td>
<td>I</td>
<td>Shiga toxin-associated</td>
<td>IV</td>
<td>MCP mutations</td>
<td>III</td>
<td></td>
<td></td>
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<tr>
<td>Cyclosporine/Tacrolimus</td>
<td>III</td>
<td>S. pneumoniae associated</td>
<td>III</td>
<td>TMA, drug-associated</td>
<td></td>
<td></td>
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<tr>
<td>Gemcitabine</td>
<td>IV</td>
<td>TMA, drug-associated</td>
<td>Ticlopidine</td>
<td>I</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Quinine</td>
<td>IV</td>
<td>Ticlopidine</td>
<td>I</td>
<td>Clopidogrel</td>
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<td></td>
<td></td>
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<tr>
<td>TMA, hematopoietic stem cell transplant–associated</td>
<td>III</td>
<td>Clopidogrel</td>
<td>III</td>
<td>Calcineurin inhibitors</td>
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<td></td>
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<td>Gemcitabine</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
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<td>Gemcitabine</td>
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<tr>
<td>Quinine</td>
<td>IV</td>
<td>TMA, hematopoietic stem cell transplantation–associated</td>
<td>III</td>
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<td>TMA, hematopoietic stem cell transplant–associated</td>
<td>III</td>
<td>Shiga toxin–mediated</td>
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<td>Refractory</td>
<td>III</td>
<td>Severe neurological symptoms</td>
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<td>S. pneumoniae</td>
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Abbreviations: HUS, hemolytic uresic syndrome; TAM, transplant-associated microangiopathy; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.
In 1956, Dr. E. Donnall Thomas reported some of the first attempts at bone marrow transplantation from a variety of cellular sources. In his conclusion, Dr. Thomas stated that:

“In an atomic age, with reactor accidents, not to mention stupidities with bombs, somebody is going to get more radiation than is good for him. If infusion of marrow can induce recovery in a mouse or monkey after lethal radiation, one had best be prepared with this form of treatment in man.”

Radiation accidents and nuclear warfare were the prevailing concern, and bone marrow stem cells were largely being studied as a countermeasure against lethal damage. Dr. Thomas also astutely commented, “The leukemic patients who need radiation and bone marrow… deserve immediate consideration. From helping them, one will be preparing for the atomic disaster of tomorrow.”

Remarkably, the method of conditioning a patient for bone marrow transplantation has not changed much since the original studies; doses of irradiation and/or chemotherapeutic agents are used to clear the marrow space of resident hematopoietic and immune cells, allowing the new cells to engraft in the limited niches available. While this is certainly acceptable after a radiation-related mass-casualty event, or after the treatment of an aggressive malignant disease, using this “bomb” approach results in toxicities that normally limit the use of stem cell transplantation to only a fraction of the patients who could potentially benefit.

With the emergence of developing gene therapies for nonmalignant disease, and increasing evidence of the potential curative option for many other diseases, a less toxic, more targeted conditioning approach is needed to broadly expand transplantation to these patient groups. Recently, two independent teams have published conditioning methods based on antibody targeting.

Dr. Rahul Palchaudhuri and colleagues report on the use of an immunotoxin, created by conjugating a CD45 antibody with saporin, which they term CD45-SAP (Figure, a and b). Saporin is a toxin in the ricin family, but unlike ricin it lacks the ability to enter a cell on its own, and instead must be conjugated to an antibody or ligand capable of internalization. Given that CD45 is expressed exclusively in the hematopoietic system, this targeted approach allowed for depletion of the bone marrow space, without unintended off-target toxicities. In mice, a single treatment of CD45-SAP followed by transplantation of 10 million whole bone marrow cells (roughly 2% of the total marrow of a mouse) resulted in 94 percent chimerism and complete, multilineage engraftment. Remarkably, when the same dose of CD45-SAP was given to mice, with no subsequent stem cell transplant, all of the mice recovered, demonstrating that the CD45-SAP is capable of conditioning to allow for high levels of engraftment, without being permanently myeloablative. Analysis of the bone marrow vasculature demonstrated no damage, in contrast to sublethal irradiation, suggesting preservation of the hematopoietic niche. Additionally, much of the thymic tissue was preserved, with a demonstrated increase in de novo T cell production. Using a mouse model of sickle cell anemia, the researchers also demonstrated that CD45-SAP was able to effectively condition, and a subsequent transplantation resulted in correction of the disease phenotype.

While CD45 is exclusively expressed in hematopoietic cells, it is not restricted to just stem and progenitor cells, but is widely expressed across all of the nucleated blood cells. In the autologous gene therapy setting, it may be more desirable to just specifically remove stem and progenitor cells, while preserving immune cell function, given the reduced chance of graft rejection since the transplanted stem cells would be of host origin. To specifically target stem and progenitor cells, a prior study had focused on antibody targeting of the c-kit receptor with the antibody ACK2. This report showed the ability to achieve modest amounts of engraftment after transplantation with high doses of purified stem cells. Surprisingly, this conditioning method only worked in immunocompromised mice and did not work in immunocompetent animals.

To boost the effectiveness of c-kit targeting and to apply the conditioning method to immunocompetent mice, Dr. Akanksha Chhabra and colleagues recently coupled the ACK2 antibody with antigen of CD47 (Figure, c and d). Acting as a “don’t eat me” signal, CD47 is present on stem cells and a wide variety of other immune cells and prevents phagocytosis and antigen presentation from macrophages and dendritic cells. Prior work in tumor biology has shown that blocking CD47 enhances tumor antibody opsonization, so the authors reasoned that similar enhancements could be made with the c-kit targeting antibody. When ACK2 was given on its own in immunocompetent C57Bl/6 mice there was no depletion of stem cells, and only modest enhancements of conditioning were seen. However, when the combination of ACK2 with the mouse-specific CD47 antagonist CV1mb resulted in robust depletion of phenotypically defined stem and progenitor cells and a marked clearance of the bone marrow space. When these mice then received transplants with stem and progenitor cell-enriched bone marrow for three consecutive days after the conditioning treatment, approximately 60 percent chimerism was achieved 20 weeks after transplantation, demonstrating that the combined treatment approach effectively increased the efficacy of c-kit targeting in immunocompetent animals. In an effort to expand this approach to a broader group of patients, who would likely receive an allogeneic graft, the researchers used a mouse model of minor histocompatibility mismatch. When Balb/c mice were treated with the ACK2/anti-CD47 regimen, along with a regimen of anti-CD4/CD8 antibodies to deplete T cells, they were able to achieve approximately 20 percent stem cell chimerism after a purified stem cell transplant from the mismatched B10D2 mice.

These new, targeted conditioning approaches come at an exciting time for stem cell transplantation, in which the potential patient pool could be remarkably expanded with the advent of new gene therapy and editing strategies. Unlike the bomb-like approaches developed since the procedure’s beginnings, these SWAT teams of specific antibodies may allow for conditioning regimens that are not only nongenotoxic, but that may allow for almost near-outpatient treatment.


Dr. Jonathan Hoggatt is an equity stakeholder in Magenta Therapeutics.

Protocol schematics. a) Schematic of CD45-SAP conditioning protocol. Mice were treated with 3 mg/kg CD45-SAP and transplanted with 107 bone marrow cells two to 12 days later. b) Long-term assessment of peripheral blood chimerism after transplantation eight days following CD45-SAP conditioning. c) Schematic of combination ACK2 and CV1mb conditioning protocol. Mice were treated once with 500 μg ACK2 and 500 μg CD47-SAP for five days. d) Frequency of donor-derived hematopoietic stem cells 24 weeks after transplantation. Reprinted by permission from Macmillan Publishers Ltd; Nature Biotechnology, vol. 34, pp 738-745, 2016; and with permission from AAAS; Science Translational Medicine, vol. 8, pp 351ra105, 2016.
Congress Passes Short-Term Funding to Keep Federal Government Open Through December 9

On the eve of recessing for the elections and with just two days left to spare before the end of fiscal year (FY) 2016, Congress passed a short-term continuing resolution (CR) to fund the government through December 9. The CR, which will fund the government at current levels for two months, averted a politically calamitous government shutdown that both parties were trying to avoid. Although the long-term funding of federal agencies and programs remains uncertain as this issue of The Hematologist goes to press, congressional leaders are expected to begin negotiations in an attempt to complete work on the FY 2017 budget prior to the expiration of the CR on December 9. As the appropriations process slowly makes its way through Congress, there are positive signs for National Institutes of Health (NIH) funding. During the summer, the Senate Committee on Appropriations proposed a $2 billion funding increase for the NIH during FY 2017, which, if approved, would bring the total funding for NIH to $34.1 billion. The House Appropriations Committee recommended a smaller increase in funding of $1.25 billion over current levels. These two numbers, as well as funding levels for nearly all other federal programs and agencies, will need to be reconciled before a final funding bill is passed.

As Congress continues efforts to pass a FY 2017 budget, ASH will carry on in its advocacy efforts, urging lawmakers to reach a bipartisan agreement that allows for sustainable increases in biomedical research funding. All members of Congress need to hear from their constituents about the need to secure viable and predictable growth for NIH, recognizing the value of biomedical research. To send a letter to your Representative and Senators about why NIH funding is important to you and your research, please visit www.hematology.org/NH.

ASH and Partnering Groups Launch Sickle Cell Disease Coalition & Submit Testimony to House Energy and Commerce Committee

In early September, ASH, along with more than 20 other member groups, issued the State of Sickle Cell Disease: 2016 Report and launched the Sickle Cell Disease Coalition. The goals of this partnership include amplifying the voice of the sickle cell disease (SCD) community, promoting SCD awareness, and transforming SCD care, both in the United States and across the globe. The Coalition and the Report were launched during a press event at the Newseum in Washington, DC, with opening remarks made by ASH President, Dr. Charles Abrams, followed by a panel of experts who spoke about the challenges facing those with SCD. To find out more information on these efforts, visit www.SCDcoalition.org.

The launch of the coalition was only a start to the Society’s focus on SCD, as ASH recently submitted testimony to the House of Representatives Energy and Commerce Committee at a hearing in September focused on bills that are aimed to improve public health, including H.R. 1407, the Sickle-Cell Disease Research, Surveillance, Prevention and Treatment Act of 2015. The legislation, introduced by Representatives Danny Davis (D-IL) and Michael Burgess (R-TX), would increase research, surveillance, prevention, and treatment for SCD within the Department of Health and Human Services. ASH’s testimony stated support for the bill and also recommended strengthening and expanding current federal efforts to help ensure that individuals living with SCD receive adequate care and treatment. Specifically, ASH noted that the following priorities would be important components of any legislative package addressing SCD:

- Authorization of the Department of Health and Human Services’ Interagency Working Group on SCD to coordinate efforts among federal agencies
- Enhancement of the Centers for Disease Control and Prevention’s SCD outreach and education programs on SCD and SCD trait for patients and providers
- Improvement of access to high quality care via demonstration projects at CMS and development of best practices
- Provision of incentives for drug development for SCD within the Food and Drug Administration (FDA, H.R. 1357, Advancing Hope Act of 2015)

Additionally, we are pleased to report that as Congress was about to adjourn for recess in September, both the House and Senate approved one of ASH’s key advocacy interests—an extension of the Advancing Hope Act of 2015 (S.B. 1878 and H.R. 1537)—through December 31, 2016. This legislation is an important part of the policy package for which ASH continues to advocate. The Advancing Hope Act expands the FDA’s priority review voucher program for rare pediatric diseases to include treatments for SCD and pediatric cancers. President Barack Obama signed it into law on September 30.
IDH1-Mutant Leukemias Impair DNA Damage Repair Due to TET2-Independent Downregulation of ATM


One of the most fascinating findings from genomic studies of leukemia from the last 10 years is the discovery of recurrent mutations in isocitrate dehydrogenase 1 (IDH1), IDH2, and ten-eleven translocation 2 (TET2) that have convergent effects on DNA methylation.1 Mutations in IDH1, IDH2, and TET2 are each mutually exclusive of one another and, in total, account for 30 to 60 percent of patients with myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), and other myeloid malignancies. Mutations in IDH1 and IDH2 confer a change-of-function of these enzymes, causing them to convert α-ketoglutarate (αKG) to the oncometabolite 2-hydroxyglutarate (2HG). 2HG competitively inhibits αKG-dependent enzymes, including the methylcytosine dioxygenase enzyme TET2. Since TET2 loss-of-function mutations occur in the same spectrum of hematologic malignancies as IDH1/2 mutations, and because TET2 loss is tightly linked to aberrant self-renewal of hematopoietic stem cells, it has been largely presumed that IDH1/2 mutations promote leukemogenesis by disabling TET2. At the same time, many lines of evidence suggest that IDH1/2 mutations may not be equivalent to TET2 loss. First, there are more than 80 αKG-dependent enzymes beyond TET2. This notably includes the other TET enzymes (TET1 and TET3), the Jumonji C (JmC) domain–containing family of histone lysine demethylases, and numerous prolyl and lysyl hydroxylases (Figure). Additionally, IDH1, IDH2, and TET2 mutations are each associated with differing clinical outcomes of AML and their own spectrum of coexisting mutations. Therefore, there is a need to dissect potential distinct features of the pathogenesis of IDH1- versus TET2-mutant leukemias.

In a recent article, Dr. Satoshi Inoue and colleagues identify impaired DNA damage repair as a unique oncogenic property of IDH1-mutant leukemias, distinct from that of TET2-mutant cells. By performing mass cytometry of hematopoietic cells from Idh1R132H knock-in mice, they identified decreased levels of phosphorylated ataxia telangiectasia mutated (ATM) in bone marrow progenitors from IDH1-mutant mice relative to controls. ATM is a kinase that is recruited to double-stranded DNA breaks and plays a role in cell cycle delay during DNA repair. DNA damage accumulated in the progenitor compartment of aged IDH1-mutant mice, but not TET2 knockout (KO) mice, as noted by increased accumulation of DNA double-stranded breaks, the phosphorylated histone variant H2AX (γ-H2AX), and tumor suppressor p53-binding protein 1 (53BP1). Furthermore, although Idh1 R132H knock-in and TET2 KO mice both develop a phenotype resembling human MDS, the authors found reduced numbers of long-term hematopoietic stem cells (LT-HSCs) only in the Idh1 R132H-knock-in mice. The magnitude of reduction in LT-HSCs also increased with age of the mice, suggesting that decreased ATM impairs the DNA damage response (DDR), leading to the accumulation of unrepaired double-strand breaks over time that potentially trigger apoptosis.

In an attempt to explain the decreased levels of ATM seen in progenitors and LT-HSCs of IDH1-mutant mice, the investigators first looked for DNA hypermethylation at the ATM promoter because IDH1/2- and TET2-mutant cells are marked by DNA hypermethylation. Although there was an increase in DNA methylation at the majority of CpG islands in the genome, there were no significant alterations at the ATM promoter, specifically compared with controls in Idh1 mutant mice. However, chromatin state at the locus of ATM was found to be more compact compared with controls, with an increase in the transcriptionally repressive histone modification histone H3 lysine 9 tri-methylation (H3K9me3). Interestingly, the JmC-domain–containing family of histone lysine demethylases responsible for removing H3K9 methyl marks is inhibited by 2HG, as noted earlier, thus establishing a possible link between IDH1 and low ATM levels. Furthermore, a pharmacologic inhibitor of H3K9 methyltransferase largely restored ATM mRNA expression.

This work provides valuable insights into the biology of mutant IDH1 in a myeloid-specific context, with the additional effect of aging, and highlights one of the TET2-independent consequences of 2HG. Given that there are many additional αKG-dependent enzymes beyond TET2 and the Jumonji family of histone lysine demethylases, it is quite likely that there are many additional examples of biological pathways that are specific to IDH1/2-mutant cells. Moreover, distinct clinical associations have been repeatedly observed comparing IDH1R132H-, IDH2R140Q-, and IDH2R172K-mutant patients, possibly related to differences in 2HG produced by each mutation.3 It will therefore be important to determine whether the findings related to impaired DNA damage response in IDH1R132-mutant cells observed here are also seen in IDH2R140Q- and R172K-mutant cells. Finally, inhibitors of mutant IDH1 and IDH2 are now entering phase III testing, with promising results noted in earlier stage trials. However, single-agent therapy does not yet seem to provide durable remissions. If the results from Dr. Inoue and colleagues are reproduced and validated in humans, this finding could offer an opportunity to explore DNA repair inhibitors in combination with IDH inhibitors with the goal of depleting the leukemic stem cell pool to achieve a state of negative minimal residual disease.


JUSTIN TAYLOR, MD, AND OMAR ABDEL-WAHAB, MD
Dr. Taylor and Dr. Abdel-Wahab indicated no relevant conflicts of interest.
Acute lymphoblastic leukemia (ALL) is the most common malignancy diagnosed in children. The survival rates of ALL have greatly improved throughout the past several decades thanks to research by cooperate working groups, with overall five-year survivals now approaching 90 percent—a true success story in medicine. Yet despite this increase in survival, conventional cytotoxic chemotherapy is relatively ineffective at initial high-risk (HR) ALL subtypes, including patients who suffer early bone marrow relapse. Additionally, even standard-risk (SR) patients still relapse. Recently, two large clinical trials of pediatric B-cell precursor ALL were studied prospectively by the same group of investigators who demonstrated that integration of genetic and clinical risk factors enables improved patient stratification and outcome.

In their article, Dr. Anthony Moorman and colleagues integrated copy-number alteration (CNA) data from the eight most commonly deleted genes (IKZF1, CDKN2A/B, PAX5, EBF1, ETV6, BTG1, RB1, and PARK1) subordinately with established chromosomal abnormalities to initial diagnosis of B-ALL to develop a two-tier genetic classification by evaluating 809 ALL97/99 study patients and validating using 742 United Kingdom (UK) ALL2003 trial patients. Good-risk genetic features included ETV6-RUNXI, high hyperdiploidy, normal copy-number status for all eight genes, isolated deletions affecting ETV6/PAX5/BTG1, and ETV6 deletions with a single additional deletion of BTG1/PAX5/CDKN2A/B. All other genetic features were classified as poor risk. They found that 75 percent of UKALL-2003 patients had a good-risk genetic profile and a significantly improved event-free survival (EFS; 94%) compared with patients with a poor-risk genetic profile (EFS of 79%), and they further identified a large subset of children suitable for treatment de-intensification.

Current risk stratification in B-ALL is primarily based on CR1 duration. In the article by Dr. Julie A.E. Irving and colleagues, the authors comprehensively evaluated the spectrum and frequency of chromosomal abnormalities, CNAs, and sequence mutations including key exons of the TP53, NRAS, KRAS, PTPN11, FLT3, and CBL genes, by analyzing cytogenetic data from 427 children with relapsed B-ALL treated on the international trial, ALLR3, and screened 238 patients with a marrow relapse for selected CNAs and mutations. Patients were assigned to three clinical risk groups (SR, intermediate-risk [IR], or HR) at relapse according to immunophenotype, site of relapse, and time to relapse, with shorter CR1, T-ALL, and marrow involvement linked to poor outcome after relapse. SR and IR were combined as “SR.” Cytogenetic testing at diagnosis and/ or relapse was used to classify patients into three previously defined mutually exclusive cytogenetic risk groups: 1) good risk (CYTO-GR)—high hyperdiploidy (HeH) and ETV6-RUNXI; 2) IR (CYTO-IR) — TCF3-PBX1, IGH translocations, and B-other (none of these established abnormalities); and 3) HR (CYTO-HR) — BCR-AEL1, KMT2A (MLL) translocations, near haploidy, low hyperdiploidy, AMP21, TCF3-HLF. All of the 245 patients tested had concordant cytogenetic results at both diagnosis and at the time of marrow relapse.

This study demonstrated that cytogenetic risk groups were predictive of outcome postrelapse; survival rates at five years for patients with good risk, IR, and HR cytogenetics were 69 percent, 47 percent, and 26 percent, respectively (p < 0.001). The cytogenetic, CNA, and mutational profile of clinical SR and HR patients was distinctive (Figure). SR patients were enriched for ETV6-RUNXI, HeH, ETV6 and RB1 deletions, and PTPN11 mutations, in contrast, TCF3-PBX1, KMT2A translocations, haploidy, low hyperdiploidy, TCF3-HLF, TP53 alterations, and NR3C1 deletions were more frequent among HR patients. CDKN2A/B, IKZF1, PAX5, and KRAS alterations were equally prevalent among SR and HR patients. The outcome of HR patients was universally poor, and none of the genetic alterations were associated with a superior outcome.

Among clinical SR patients, those with CYTO-GR and CYTO-HR had the highest risk of progression/death compared with CYTO-IR patients, respectively. The most prevalent secondary abnormalities among SR patients were deletions or alterations of CDKN2A/B, IKZF1, and PAX5, which were not associated with response or outcome. TP53 mutations and 17p13 deletions occurred at an increased frequency in the CYTO-HR groups at initial diagnosis, and they were associated with a poor outcome at relapse. SR patients with a TP53 alteration also had an inferior outcome and an increased risk of death. NR3C1/BTG1 deletions were more common among cytogenetic and clinical HR patients and associated with an inferior outcome in both SR and HR groups, with the strongest effect in the HR group correlating with a high rate of induction failure and death. The good outcome of ETV6-RUNXI and HeH was not adversely affected by ETV6 deletions and PTPN11 mutations. However, the presence of NRAS mutations was associated with a threefold increased risk of progression/death among SR HeH patients.

CYTO-HR patients had a uniformly poor outcome, with high rates of induction, failure/death, and second relapse, and they may benefit from alternative therapeutic strategies. The five-year progression-free and overall survival rates for SR patients with CYTO-HR were 25 percent (95% CI, 8%-46%) and 29 percent (95% CI, 9%-52%), which are almost identical to those of HR patients overall, and not different from those of CYTO-HR patients classified as HR. This is the first study examining the prognostic effect of CYTO-HR abnormalities by clinical risk group in relapsed ALL, and it indicates that all CYTO-HR patients should be treated on future HR protocols regardless of clinical risk stratification.

Overall, this large cohort study represents the most comprehensive genetic study of relapsed childhood B-ALL and provides compelling evidence that refining the risk classification by integrating genetic and clinical risk factors improves patient stratification and outcome in the relapse setting.
Progress in the treatment of acute lymphocytic leukemia (ALL) in adults has lagged behind that in children, with cure rates of approximately 40 to 50 percent. Outcomes following relapse are dismal, despite the delivery of intensive chemotherapy with or without hematopoietic stem cell transplantation (HSCT), and the limits of tolerability have been reached with conventional cytotoxic therapies. The development of alternative treatment approaches has accordingly been a high priority, and several promising new immune therapies have been developed recently.1-3 Adding to this experience, Dr. Hagop M. Kantarjian and colleagues have reported their findings from a trial investigating inotuzumab ozogamicin, a humzired anti-CD22 monoclonal antibody bound to calicheamicin, in adults with relapsed or refractory ALL.

Investigators from 18 international sites conducted the INO-VATE phase III study in adults 18 years or older with relapsed or refractory CD22-positive B-cell ALL undergoing first or second salvage therapy. Patients were randomly assigned 1:1 to treatment with inotuzumab ozogamicin versus one of three standard cytotoxic chemotherapy regimens of investigator choice (Figure). Patients aged 18 to 79 years (median, 47 years) participated in this trial. Inotuzumab ozogamicin was administered weekly for three doses per 21- to 28-day cycle for up to six cycles. Those assigned to conventional chemotherapy received up to four cycles of standard chemotherapy, and any patient in either treatment group who achieved complete remission (CR) could undergo HSCT.

The primary endpoints for this study were rates of CR, which included CR with incomplete hematologic recovery (CRi), and overall survival. Patients receiving inotuzumab ozogamicin had a significant improvement in several outcome measures compared with the standard chemotherapy group. Among the first 218 patients comprising the remission analysis population (intention-to-treat), the CR rates for the inotuzumab ozogamicin group were 80.7 percent versus 29.4 percent, P<0.001 in the standard therapy group. Similar significant improvements in CR rates with inotuzumab ozogamicin were also observed in an as-treated analysis. Among those achieving CR, a significantly higher percentage of patients in the inotuzumab ozogamicin group had a minimal residual disease (MRD) burden below a threshold of 0.01 percent by flow cytometry (78.4% vs. 28.1%, P<0.001), and a significantly higher percentage proceeded to HSCT. The duration of remission, progression-free survival, and overall survival was also longer with inotuzumab ozogamicin compared with standard chemotherapy in the 1,326 patients included in the intention-to-treat survival analysis. The rate of two-year overall survival was 23 percent in the inotuzumab ozogamicin group and 10 percent in the standard therapy group. Overall, inotuzumab ozogamicin was well tolerated. The only significant difference compared with the other regimens was a higher rate of infusion-related reactions and veno-occlusive disease of the liver, which was more common in the inotuzumab ozogamicin group versus the standard chemotherapy group (11% vs. 1%), and the risk was highest among patients who received the drug prior to or following HSCT with a dual alkylator conditioning regimen. The toxicities observed with inotuzumab ozogamicin were otherwise comparable to those observed with standard chemotherapy.

This article describes a highly promising new monoclonal antibody therapy for CD22-positive B-cell ALL. The significant improvement in CR rates with inotuzumab ozogamicin is a key finding because attaining CR is generally viewed as prerequisite to HSCT, which is currently the only curative modality otherwise comparable to those observed with standard chemotherapy.

Inotuzumab ozogamicin

Starting dose 1.8 mg/m²/cycle

- 0.8 mg/m² on day 1;
- 0.5 mg/m² on days 8 and 15 of a 21-28 day cycle;
- 8 cycles

Standard of Care

-FLAG,
- Cytarabine plus mitoxantrone,
- High-dose cytarabine
- 4 cycles

Treatment schema. Inotuzumab ozogamicin dose reduced to 1.5 mg/m²/cycle once complete remission/complete remission with incomplete hematologic recovery was achieved. Abbreviations: ALL, acute lymphoblastic leukemia; FLAG, fludarabine, cytarabine, and granulocyte colony-stimulating factor. Adapted with permission from N Engl J Med. 2016;375:740-753.


Dr. Raetz indicated no relevant conflicts of interest.

Elizabeth K. O’Donnell, MD, and Noopur Raji, MD
Dr. O’Donnell and Dr. Raji indicated no relevant conflicts of interest.
βTraxler EA, Yao Y, Wang YD, et al. A genome-editing strategy to treat CRISPR-Cas9 Genome Editing: With a Little Help reversed the switch from fetal to adult globin in CD34+ HSPCs from normal individuals that contains a CCAAT box and a direct repeat, which likely recruits transcriptional activator or repressor proteins. Hereditary persistence of fetal hemoglobin (HPFH) is a benign genetic condition caused by mutations that attenuate the switch from fetal γ-globin to adult β-globin, which results in increased expression of fetal hemoglobin (HbF). Clinical symptoms of SCD or β-thalassemia are alleviated in patients who have inherited HPFH. The formation of pathologic rigid ΗSωs polymers under deoxygenated conditions in SCD is inhibited by the presence of HbF. These findings prompted a gene manipulation strategy to recapitulate one of the HPFH mutations, which would induce therapeutic levels of HbF.

Dr. Elizabeth Traxler and colleagues focused on a 13-nucleotide deletion from –102 to –114 within the HGB1 promoter, which leads to HbF levels of approximately 30 percent in subjects heterozygous for the mutation. The 13-nucleotide sequence recruits transcriptional repressor proteins, and individuals with this type alleles exhibit levels lower than 1 percent HbF. The researchers used CRISPR-Cas9 technology to edit this region in a HUDEP–2 human erythroblast cell line expressing predominantly HbA. They engineered a lentiviral vector to express an mCherry marker, Cas9, and two different nonoverlapping guide RNAs (gRNA-1 and gRNA-2) flanking the target sequence. Transduced cells exhibited an increase in HbF protein; in these cells, there was a commensurate increase in expression of γ-globin mRNA and a decrease in expression of β-globin mRNA. Mock-infected cultures and control cultures expressing only Cas9 had no HbF. gRNA-1 induced a greater amount of HbF than gRNA-2, but since both were effective, it suggested an on-target rather than an off-target phenomenon. The next step involved editing peripheral blood CD34+ hematopoietic stem and progenitor cells (HSPCs) from two healthy adults using the same vectors. Transduced cells expressing mCherry were enriched by cell sorting and HbF levels evaluated after erythroid differentiation. Erythroid progeny cells expressing gRNA-1 again produced a better response and showed an increase in HbF levels from 5 percent to 20 percent, and the number of HbF positive cells rose from 18 percent to 58 percent. Relative levels of HbF mRNA confirmed that the switch from γ to β-globin had been reversed.

These promising results led the research team to test the potential therapeutic effect by transducing CD34+ HSPCs from three patients with SCD using the gRNA1-lentiviral vector, which increased HbF cells to 90 percent. Culturing these edited cells under hypoxic conditions of 2 percent O2 reduced sickling to 4 percent. Residual HbS polymerization could result from inefficient editing or from mutations that did not induce HbF. To characterize the mutations induced by CRISPR-Cas9 double stranded DNA breaks and error prone nonhomologous end joining, the researchers used polymerase chain reaction and deep sequencing of a 431-nucleotide region encompassing the predicted cleavage sites in the HGB1 or HGB2 genes. This revealed a predominance of the targeted 13-nucleotide deletion and equal mutation rates in the two homologous γ-globin genes, as well as 30 other on-target smaller indels. Simultaneous double-stranded DNA cleavage at gRNA-1 recognition sites in the promoters of HBG1 and HBG2 may result in poising of the two ends with loss of the intervening 5.2 kb of genomic DNA. Human CD34+ cells that had been transduced with 10 μg of the Cas9-gRNA1- vector were examined by quantitative polymerase chain reaction, but there was no evidence of this large detrimental deletion. Bioinformatic analyses predicted several off-target sites, but deep sequencing of these transduced cells showed no indels in the top 15 sites. This study has revealed several important findings: 1) the 13-nucleotide region in the promoters of the HGB1 and HGB2 globin genes is a co-regulatory element that contains a CCAT box and a direct repeat, which likely recruits transcriptional repressor proteins; 2) deletion of this region by CRISPR-Cas9 genome editing partially reversed the switch from fetal to adult globin in CD34+ HSPCs from normal individuals and patients with SCD; and 3) increased expression of HbF in edited SCD cells inhibited polymerization of HbS and the pathologic sickling of these cells under hypoxic conditions. These exciting results thus provide proof of principle for a therapeutic genome editing strategy whereby a benign yet occurring mutation is recapitated ex vivo in cells from patients with SCD. This study provides a framework for further refinement of the editing procedure and the application to other β-hemoglobinopathies.

Targeting PD-1 in Classical Hodgkin Lymphoma


Recent evidence suggests that classical Hodgkin lymphoma (cHL) is ideally suited to therapy with checkpoint inhibitors. In Reed-Sternberg cells, the most uniform upregulation of programmed death ligands 1 and 2 (PD-L1 and PD-L2) result from copy number alterations in chromosome 9p24.1. The clinical responses and correlative studies in the phase 1 studies of nivolumab and pembrolizumab in relapsed and refractory Hodgkin lymphoma have clearly borne out this hypothesis. In the nivolumab trial reported by Dr. Anas Younes and colleagues, 80 patients with relapsed cHL whose disease recurred following autologous stem cell transplantation and had progressed or failed to respond to brentuximab vedotin were treated with 3 mg/kg of study drug every two weeks until progression. Patients were heavily pretreated, having received a median of four prior therapies. With a median follow-up of approximately nine months, the overall and complete response rates were 66 percent and 9 percent, respectively. Thirty-one patients were enrolled on the pembrolizumab study reported by Dr. Philippe Armand and colleagues. Eligible patients were required to have received prior brentuximab vedotin and undergone autologous stem cell transplantation (ASCT) unless ineligible or declined. The drug was administered at a dose of 10 mg/kg every two weeks until disease progression. More than half of the patients had received five or more prior therapies. Seventy-one percent of patients had failed autologous stem cell transplantation (ASCT). In terms of the activity of pembrolizumab, it was remarkably consistent with that of nivolumab. The overall response rate was 65 percent. Seventy-three percent of patients who had undergone prior ASCT and 44 percent of those who were deemed ineligible for transplantation responded. Complete remissions were seen in 18 percent overall, in 14 percent of those with a prior ASCT, and in 22 percent of those with no prior ASCT. Overall, therapy in both trials was well tolerated with fatigue, infusion reaction, and fever being the most common adverse events in the nivolumab study. Hypothyroidism, diarrhoea, nausea, and pneumonitis were the most common toxicities with pembrolizumab. Correlative studies in the nivolumab trial were performed on tissue biopsies from 45 patients. Fluorescence in situ hybridisation analyses of Reed-Sternberg cells revealed polysomy, copy gain, and amplification of 9p24.1 in 16 percent, 58 percent, and 27 percent of patients, respectively. Additionally, the JAK-STAT pathway was activated in all samples, as evidenced by staining of phosphorylated STAT3. Interestingly, the investigators demonstrated a correlation between response and the level of 9p24.1 alteration and of PD-L1 expression. None of the patients with the lowest level (polysomy) achieved a complete remission. Of the patients who experienced progressive disease, none had amplification. Additionally, patients who achieved a complete remission had the highest levels of PD-L1 staining and none had polysomy.

In the pembrolizumab study, tissue specimens were evaluable from 16 patients at the time of study enrollment. By immunohistochemical staining, 94 percent expressed PD-L1, and 90 percent of the 10 patients assessed for PD-L2 were positive. Nine patient samples were assessed for T-cell subsets by flow cytometry. Comparing baseline and post-cycle 7 samples, the absolute numbers of T-cells, CD4, CD8, and NK cells all rose during therapy. Additionally, using NanoString technology, paired samples from 19 patients were analyzed. IFN-γ induced genes increased with treatment, as did gene signatures related to T-cell receptor signaling and other immune-related genes. Given the small number of samples, the changes were not predictive of response.

The phase 1 clinical trials of nivolumab and pembrolizumab demonstrate the efficacy of targeting PD-1 in cHL. The question now is how to integrate these agents into the overall therapeutic approach to the disease. Cure rates with existing, standard treatments are high, particularly in early-stage disease. Although PD-1 inhibitors are active even in the most heavily pretreated patients, the complete remission rates are low and the long term durability of response has yet to be seen. Future studies are needed to determine which patients require these agents, as well as the optimal duration and combination strategies.
Telomeres are specialized DNA-protein structures that protect chromosome ends from degradation and fusion. They are composed of long stretches of repetitive TTAGGG sequences that are bound by a group of proteins called shelterin. As the DNA replication machinery cannot fully copy the ends of chromosomes, telomeres progressively shorten with each cell division, eventually triggering cell senescence. Telomerase is a ribonucleoprotein enzyme complex capable of de novo synthesis of telomeric repeats, and in association with a number of other protein functions, helps maintain the length of telomeres in somatic and germline cells, including hematopoietic stem cells. Moreover, this repair process is incomplete, and telomere length attrition occurs normally with each cell division.1 Telomeres, or short telomere syndromes, are a group of Mendelian disorders that share an underlying molecular finding of short telomere lengths. In effect, these patients age prematurely and clinically manifest with variable complications that may include bone marrow failure (potentially due to stem cell exhaustion), and lung and liver disease. Premature telomere shortening is also observed in presymptomatic, immunologically mediated, aplastic anemia, potentially as a consequence of increased cell turnover and proliferation to compensate for hematopoietic stem cell depletion.

Androgens have been used to improve cytopenias in inherited and acquired bone marrow failure for decades.2 3 Androgens upregulate telomerase reverse transcriptase expression (TERT) and telomerase activity,4,5 which may account for a component of this hematologic response.

Dr. Danielle M. Townsley and colleagues recently reported the results of the first prospective phase I/II study to evaluate the use of androgen therapy in short telomere disorders.4 All patients had age-adjusted telomere lengths ≤1.6 centromeres, and/or a <0.9 T/S ratio. During danazol therapy, they also had at least a single-lineage cytopenia or pulmonary fibrosis, or both. Telomere length was measured in peripheral blood leukocytes by real-time quantitative polymerase chain reaction (qPCR), and in a subset of patients, also by fluorescent in situ hybridization (flow-FISH). Patients received 800 mg of oral danazol daily in divided doses. Twenty-seven patients were enrolled on the study, 24 received treatment, and 12 were evaluable at the time of analysis. Of the 27 patients enrolled, 12 had mutations in TERC, three had mutations in DKC1, and one had a mutation in RETEL1. Among the 12 evaluable patients at 24 months, 10 carried pathogenic mutations in a telomere maintenance or repair gene. The study was stopped early due to the unexpected high level of efficacy in achieving the primary efficacy endpoint of a reduction in telomere length attrition to ≥96 or fewer base pairs per year at 24 months follow-up; this was observed in 11 of the evaluable patients. This endpoint can be considered in the context of what the authors estimate as an expected rate of telomere loss of 60 base pairs per year in normal patients versus 120 base pairs per year in patients with telomerase gene mutations. Telomere elongation was noted at all time points during danazol treatment. The mean increase in telomere length compared with baseline was 386 base pairs (95% CI 178-593) after 24 months of treatment. Patients also demonstrated increases in their peripheral blood counts. Specifically, a hematologic response (≥0.5 g/dl hemoglobin increase, >50% reduction in transfusion requirement, ≥10% platelet count increase, or ≥0.9 x 10^12 neutrophil count increase) was observed in 79, 81, 78, and 83 percent of patients after two, six, 12, and 24 months of treatment, respectively.

The most common suspected treatment-related adverse events were elevations in liver enzyme values in 11 (41%) of 27 patients, muscle spasm or cramps in nine (33%) of 27 patients, edema in seven (26%) of 27 patients, and high cholesterol in seven (26%) of 27 patients.

The results of this prospective study confirm earlier studies dating to the mid-20th century that demonstrate that clinical improvement in blood counts can be associated with treatment through the restoration of telomere lengths in patients with short telomere syndromes. However, the observation of telomere elongation in circulating leukocytes in treated patients stands in contrast with an earlier retrospective study of androgen therapy in a small number of patients with short telomere syndromes,4 and telomere length attrition occurs normally with each cell division.1 Telomeres, or short telomere syndromes, are a group of Mendelian disorders that share an underlying molecular finding of short telomere lengths. In effect, these patients age prematurely and clinically manifest with variable complications that may include bone marrow failure (potentially due to stem cell exhaustion), and lung and liver disease. Premature telomere shortening is also observed in presymptomatic, immunologically mediated, aplastic anemia, potentially as a consequence of increased cell turnover and proliferation to compensate for hematopoietic stem cell depletion.

Further studies with longer follow-up and more clinical evaluations are needed to determine the efficacy of androgens to treat and/or prevent other disease manifestations associated with short telomere syndromes (e.g., pulmonary and liver dysfunction). These studies are also needed to address whether there are any long-term consequences of this type of therapy in these populations of patients who may be particularly susceptible to the adverse effects of androgens given their specific underlying genetic disorder. For example, the high incidence of liver test abnormalities in this study was not observed in Fanconi anemia patients whose marrow failure was treated with androgen therapy,5 potentially reflecting a particular vulnerability to this toxicity among patients with short telomere syndromes; liver dysfunction is a known complication in short telomere syndromes.

Celebrating the ASH Scholar Awards

For more than 30 years, the ASH Scholar Awards have ensured the opportunity for promising hematologists to make the journey from training to successful, independent careers. In that time, 377 Scholar Awards have been provided, supporting not only the tangible needs (such as funding for laboratory equipment and supplies) of hematology researchers, but also helping to secure one of the most critical intangibles in any person’s career—confidence. As awardee Dr. Anupama Narla says, “It really was that next step, developing that confidence that I could do this. That was part of this community that would support me and I could work with people within it. It made me feel legitimate. It helped me set up my own lab. I earned it.” With each award conferred, these talented scholars gain the confidence and mental fortitude that comes from the recognition of their work by established experts in the field.

Along with the confidence and increased feeling of belonging comes a freedom and flexibility to take risks, pursue more unusual projects, and harness their creativity to address difficult treatment problems. “We did a series of studies and we found a couple of very interesting genetic changes were associated with particular forms of ALL,” remembers Dr. Charles Mullighan, who was awarded in 2008. “The scholar award helped take that in two directions: to push the genomic envelope to use more high-resolution and sophisticated techniques to further advance our genetic understanding, and to perform experimental work to understand how these genetic changes were cooperating in the process of leukemia development… In terms of the impact that it had on me, it was very concrete.”

And in addition to the effect scholar awards have on the individual winners, the ripple effect throughout the field is undeniable. Scholar award winners represent a dynamic group with numerous intersections across geographical areas, institutions, and mentor-mentee relationships. It becomes a piece of a wider net that supports the field and allows it to continue flourishing and providing the best care for patients with hematologic diseases. “There is connectivity between the different generations of scientists,” says Dr. Narla. “We are building on each other’s work, keeping the knowledge moving forward. These are people with whom I would like to collaborate…people I respect.”

This year in San Diego at the 58th ASH Annual Meeting, take part in a special celebration of the role ASH Scholar Awards play in the continued growth and vitality of hematology. Be on the lookout for videos, a commemorative display in the San Diego Convention Center, and the launch of a page on www.hematology.org with information on the awards and their influence over the years. And if you see someone wearing a scholar award pin or ribbon, don’t hesitate to say “congratulations.”

Save the Date for the 2017 Highlights of ASH Series

Hematologists can take advantage of the expert analysis from the 58th ASH Annual Meeting closer to home. These smaller, clinically focused meetings beginning in January 2017 provide an opportunity to hear leading experts present unbiased analysis of annual meeting abstracts and sessions. Attendees will learn more about evolving therapies, the latest treatment options, and their clinical applications. The program format is designed to offer practitioners, fellows, academicians, and allied-health professionals the opportunity to discuss some of the most rapidly evolving developments in the field. Highlights of ASH will take place in the following dates and locations:

Highlights of ASH in North America
January 13-14 – Atlanta, GA
January 20-21 – Chicago, IL, and Dallas, TX
January 27-28 – New York, NY, and Seattle, WA

Highlights of ASH Latin America
April 7-8 – Punta del Este, Uruguay

Highlights of ASH Asia-Pacific
March 10-12 – Hong Kong

For more information, visit www.hematology.org/highlights.

Submit Your Manuscript for Blood Advances

Blood Advances is the new peer reviewed, open access, electronic format journal which will debut its inaugural issue in December at the 58th ASH Annual Meeting in San Diego. Submit your manuscript online; benefits to authors include speed to publication, fast peer-review process, and a single submission fee for Blood Advances and Blood. Publication fees for all articles published in the inaugural issue will be waived. For more information, visit www.bloodadvances.org.
Testing a Novel Approach to Chemotherapy-Associated Thrombocytopenia

**STUDY TITLE:** American Trial Using Tranexamic Acid in Thrombocytopenia (A-TREAT)

**CLINICALTRIALS.GOV IDENTIFIER:** NCT02578901

**FUNDING SOURCE:** National Heart, Lung, and Blood Institute

**PARTICIPATING CENTERS:** University of Pittsburgh, University of North Carolina, University of Washington

**ACCRUAL GOAL:** 330 patients

**STUDY DESIGN:** In this double-blind, randomized, placebo-controlled trial, patients who are likely to have platelet counts of ≥10,000/µL for five days are assigned either the antifibrinolytic agent, tranexamic acid (TXA), or placebo. The thrombocytopenia must be hypoproliferative, secondary to primary marrow disorders, chemotherapy, immunotherapy, radiation and/or hematopoietic stem cell transplant. The dose of TXA is 1.0 g intravenously or 1.3 g by mouth every eight hours. Study medication is initiated once the platelet count drops below 30,000/µL, and the study period continues until the count is greater than or equal to 30,000/µL, for three consecutive days without transfusion support or for 30 days after initiation, whichever is shorter. The primary endpoints are bleeding and thrombosis throughout the study period or 30 days after initiation of study drug. Assessments will be performed daily on inpatient subjects via chart review, subject interview and physical examination. Outpatient subjects will maintain a daily diary and be seen at least weekly in clinic.

**RATIONALE:** The majority of patients with thrombocytopenia due to chemotherapy-induced marrow aplasia and primary hematopoietic stem cell disorders will experience bleeding at some point during the treatment course. While most of this bleeding is low grade, rates increase significantly when the platelet count drops below 5,000/µL, and the majority of patients require one or more platelet transfusions to remain safely above this threshold. Keeping the platelet count above any threshold is often challenging for several reasons, and even low-grade bleeding can have a negative impact on patient quality of life and resource utilization. Any intervention that could reduce rates of bleeding and/or platelet transfusions would have major safety and cost-saving implications.

**COMMENT:** The possibility that antifibrinolytic agents, which can be given either intravenously or orally, could lower the risk of bleeding and/or reduce the use of donor platelets is exciting but unproven. This pivotal, well-designed randomized trial will test the hypothesis that tranexamic acid is a safe and effective treatment for patients with thrombocytopenia due to chemotherapy-related myelosuppression or a primary hematopoietic stem cell disorder. In addition to determining whether the number of platelet transfusions or bleeding episodes is reduced, the study will provide key evidence as to whether TXA affects any clinically important increase in the risk of thrombosis.

"David Garcia, MD"

Dr. Garcia indicated no relevant conflicts of interest.

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Checkpoint Inhibition in Hodgkin Lymphoma: Time to Check at Which Point to Use It

**STUDY TITLE:** Study of Pembrolizumab (MK-3475) vs. Brentuximab Vedotin in Participants With Relapsed or Refractory Classical Hodgkin Lymphoma (MK-3475-204/KNOTE-204)

**CLINICALTRIALS.GOV IDENTIFIER:** NCT02684292

**SPONSOR:** Merck Sharp & Dohme Corp.

**ACCRUAL GOAL:** 300

**PARTICIPATING CENTERS:** 22 Centers across the United States, Europe, Japan, and Australia

**STUDY DESIGN:** This is a phase III, randomized, open-label clinical trial that compares the PD-1 inhibitor pembrolizumab with brentuximab vedotin in subjects with relapsed or refractory classical Hodgkin lymphoma (HL). The primary outcome measures are progression-free survival and overall survival. A secondary outcome measure will be the objective response rate. Pembrolizumab will be given as 200 mg doses administered intravenously on day 1 of each three-week cycle, and brentuximab vedotin will be given at a dose of 1.8 mg/kg intravenously (maximum, 180 mg per dose) on day 1 of each three-week cycle. Both treatments can be given for up to 35 cycles.

**RATIONALE:** Blockade of PD-1 with antibodies such as pembrolizumab or nivolumab has been shown to be highly effective in patients with relapsed HL. Such treatment is well tolerated and relatively easy to administer. However, these studies have been performed in patients with late stage disease, so it is not clear how they will perform in patients at an earlier stage of the disease course. The anti-CD30 antibody-drug conjugate brentuximab is effective for patients who relapse after autologous stem cell transplantation or who are not suitable for this procedure.

This study now compares the use of pembrolizumab directly against brentuximab at the same stage of disease.

**COMMENT:** Hematologists might be excused for thinking that they pioneered the introduction of almost all forms of modern cancer therapy. Single-agent chemotherapy, combination chemotherapy, monoclonal antibodies, and kinase inhibitors all have their roots in the management of leukemia and lymphoma. However, solid tumor oncology has forged a leading position in the deployment of immunotherapy. Here, the monoclonal antibody “checkpoint inhibitors” such as anti-PD-1 or anti-PD-L1 are poised to overturn the conventional approach to cancer therapy.

Within hematology, PD-1 blockade has been most effective in the treatment of relapsed classical HL (cHL). PD-L1 expression is increased in many cases of cHL through genetic amplification at chromosome 3p24.1. The pioneering study of Dr. Stephen M. Ansell and colleagues revealed a response rate of 87 percent following administration of nivolumab — another antibody that blocks PD-1. Pembrolizumab is also effective, with a 67 percent response rate seen in cHL patients for whom brentuximab has failed. However, patients in these trials had advanced disease; therefore, the exciting aspect of this study is that PD-1 blockade is being introduced earlier in the cHL treatment pathway, and in direct comparison to brentuximab. Furthermore, if the results of this study are indeed positive, it moves us closer to considering checkpoint blockade as a potential frontline therapy for HL. Such incremental improvements cannot be assumed; for example, nivolumab recently failed to show improvement against chemotheraphy for the frontline treatment of non-small-cell lung cancer (NSCLC). Additionally, although response rates to checkpoint blockade in cHL are impressive, only a minority of patients currently achieve complete remission. Checkpoint blockade is now being combined with chemotherapy in several settings, although the optimal sequential approach remains to be determined. Much work needs to be done, but if progress is maintained, we may perhaps move from ABVD to CAR-T (or perhaps ABCD-V). Now there is an abecedarian acronym to make even hematologists take note.


-- Paul Moss, PhD

Dr. Moss indicated no relevant conflicts of interest.
Laura L. Swystun and Dr. Patricia C. Law review the role of leukocytes in modulating thrombosis and discuss how leukocytes may be a novel target for antithrombotic therapy.

**AUGUST 25, 2016**


In many centers, HIV infection is considered a contraindication for autologous hematopoietic cell transplantation (AHCT) for patients with lymphoma. Dr. Joseph C. Alvarnas and colleagues report the results of a multicenter phase 2 trial of AHCT for patients with HIV-related lymphoma, demonstrating outcomes equivalent to those in HIV-negative lymphomas without loss of virucidal control of HIV.


In this review, Dr. Bernice Lo and colleagues describe two newly-characterized immunodeficiency syndromes that cause CTLA-4 deficiency. They illustrate the critical role of CTLA-4 in immune checkpoint regulation and how CTLA-4 deficiency can mimic complications of therapy with novel CTLA-4 checkpoint inhibitors.

**SEPTEMBER 1, 2016**


This paper reports a comprehensive landscape of structural gene rearrangements of the programmed death ligand (PDL) locus (Ip24.1) harboring PDL1/CDS2 and PDL2/PDCD1LG2, thus providing critical information about the breakpoint anatomy of these rearrangements in B-cell lymphoma.

**SEPTEMBER 8, 2016**


Dr. Véronique Leblond and colleagues present new recommendations for the treatment of Waldenström macroglobulinemia. They highlight the role of established therapies using rituximab, cyclophosphamide, bortezomib, and bortezomib-containing combinations, and they discuss novel treatments with BTK inhibitors, B-cell receptor inhibitors, and new proteasome and mTOR inhibitors.

**SEPTEMBER 22, 2016**


Two articles in this issue examine the clinical challenge of refractory immune thrombocytopenia (ITP). In a “How I Treat,” Adam Cuker and Cindy E. Neuenrt discuss a tiered approach to the ITP patient unable or unwilling to undergo splenectomy: progressing from established agents to investigational approaches. In the second article, Dr. Matthieu Mahévas and colleagues report on a study of 37 patients with ITP refractory to steroids, splenectomy, and thrombopoietin (TPO)-Ra mimetics. These patients often have secondary ITP with poor outcomes, but they may respond to combined TPO mimetic and immunosuppressive therapy.


Dr. Robert Chen and colleagues present the five-year follow-up of the pivotal phase 2 trial of brentuximab vedotin in 102 patients with relapsed or refractory Hodgkin lymphoma. They report an overall progression-free survival (PFS) of 22 percent; in patients achieving a complete response, overall survival and PFS were not yet reached.
A Stimulating Case of Leukocytosis
BY JOHN H BAIRD, MD1 AND JASON GOTLIB, MD, MS1
1. Division of Hematology, Stanford Cancer Institute, Stanford, CA

A 68-year-old woman with a history of chronic leukocytosis was referred for a second opinion. She has no significant past medical history. She has smoked a pack of cigarettes weekly for the past 30 years. She initially presented with a mild neutrophilic leukocytosis, which has been slowly progressive throughout the past 17 years (WBC 13.3-32.7 × 109/L; absolute neutrophil count 26.5 × 109/L at the time of referral). The hemoglobin and platelet count are normal. She has remained asymptomatic during this period and does not have palpable lymphadenopathy or hepatosplenomegaly on examination. A peripheral blood smear is shown below. What is the diagnosis?

A. Atypical chronic myeloid leukemia
B. Leukemoid reaction
C. Cigarette smoking
D. Chronic neutrophilic leukemia

For the solution to the quiz, visit The Hematologist online, www.hematology.org/Thehematologist/Images.
Universal Precautions Help Decrease Rate of Exercise-Related Death in Patient With Sickle Cell Trait

Exercise-related death has previously been associated with sickle cell trait. Evidence for this association was based initially on case reports from military recruits. Subsequently, a landmark population-based study conducted by the U.S. armed forces and published in 1987 indicated that during basic training, recruits with sickle cell trait had a relative risk of death of 2.97, when compared to those without sickle cell trait. Recently, multiple Division I football players with sickle cell trait have sustained injuries or died while practicing. On behalf of the surviving families, multiple lawsuits were filed against the National Collegiate Athletic Association (NCAA) in a landmark case in a federal court. Ultimately, the experts determined that current scientific evidence did not justify this requirement and was not consistent with good medical practice or established principles of public health ethics. Based on the expert review and discussion, ASH released a Statement on Screening for Sickle Cell Trait and Athletic Participation (www.hematology.org/Advocacy/Statements/2650.aspx) in 2012, which specifically, recommends the implementation of universal interventions to reduce exertion-related injuries and deaths because this approach can be effective for all athletes, irrespective of their sickle cell status. The policy statement notes that the NCAA's screening policy has unintended consequences, including, but not limited to harming the student athlete and the larger community of individuals with sickle cell trait if other risk factors are not considered and if the application of their mandate resulted in stigmatization and possible discrimination. Finally, the ASH policy statement calls for more biomedical and population-based research on sickle cell trait and adverse health outcomes. The provisions in the ASH policy statement are available on the ASH website (www.hematology.org/Advocacy/Statements/2650.aspx).

We now have the strongest possible evidence that implementing universal precautions to prevent dehydrating and heat-induced and exercise-induced injury and death and noted a significant decline in death for both black recruits and white recruits during basic training. Ultimately, the experts determined that current scientific evidence did not justify this requirement and was not consistent with good medical practice or established principles of public health ethics. Based on the expert review and discussion, ASH released a Statement on Screening for Sickle Cell Trait and Athletic Participation (www.hematology.org/Advocacy/Statements/2650.aspx) in 2012, which specifically, recommends the implementation of universal interventions to reduce exertion-related injuries and deaths because this approach can be effective for all athletes, irrespective of their sickle cell status. The policy statement notes that the NCAA's screening policy has unintended consequences, including, but not limited to harming the student athlete and the larger community of individuals with sickle cell trait if other risk factors are not considered and if the application of their mandate resulted in stigmatization and possible discrimination. Finally, the ASH policy statement calls for more biomedical and population-based research on sickle cell trait and adverse health outcomes. The provisions in the ASH policy statement are available on the ASH website (www.hematology.org/Advocacy/Statements/2650.aspx).

In early October 2016, ASH announced that the Exemplary Service Award would be presented to Dr. David Grimwade, who passed away on October 16. Dr. Grimwade served as a Professor of Molecular Hematology at King’s College London, and was a member of the Department of Medical and Molecular Genetics at Guy’s King’s and St. Thomas’ School of Medicine. In addition to Dr. Grimwade’s expertise in the molecular characterization of acute promyelocytic leukemia (APL), he contributed a wealth of knowledge to the identification of prognostic factors in acute myeloid leukemia (AML) and approaches for the detection of minimal residual disease.

The award was established in 1998 in recognition of ASH members whose years of service have significantly advanced the Society’s interests. Dr. Grimwade, thanks to his deep commitment and contributions to ASH training programs, specifically the International Consortium on Acute Leukemia (ICAL) and the Translational Research Training in Hematology (TRTH), was selected for the honor just prior to his passing.

ICAL is an international network that seeks to improve the care of patients with acute leukemia. The program convenes clinical investigators from three continents in the spirit of international clinical and laboratory collaboration. Since 2007, Dr. Grimwade devoted his time and energy to sharing his expertise with his Latin American colleagues through ICAL, and in 2013 he was selected by the group to chair the Laboratory and Diagnostic Activities Subcommittee. His exemplary leadership helped guide numerous laboratory personnel in ICAL member countries to reinforce their technical and diagnostic capabilities, ultimately improving the diagnosis and treatment of acute leukemia. Dr. Grimwade was also pivotal in working with his ICAL colleagues on a chemotherapy-free protocol for APL.

TRTH is a joint effort by the European Hematology Association and ASH that provides junior researchers with a unique, year-long training and mentoring experience to help strengthen their careers in hematologic translational research. As a TRTH faculty member, and ultimately a co-director for 2016, Dr. Grimwade mentored numerous trainees and junior faculty, who were impressed not only with his dedication and extensive knowledge and experience, but also his sense of humor and easygoing nature.

In his ICAL colleagues on a chemotherapy-free protocol for APL.

Dr. Grimwade passed away on October 16, 2016, and was a member of the Department of Medical and Molecular Genetics at Guy’s King’s and St. Thomas’ School of Medicine. In addition to Dr. Grimwade’s expertise in the molecular characterization of acute promyelocytic leukemia (APL), he contributed a wealth of knowledge to the identification of prognostic factors in acute myeloid leukemia (AML) and approaches for the detection of minimal residual disease.

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