ASH NEWS AND REPORTS

**Update on the ASH Research Collaborative Data Hub**

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On behalf of the ASH Research Collaborative (ASH RC) and the Data Hub, I am pleased to provide the hematology community with an update on our progress to date and plans for 2020. The ASH RC is a non-profit organization established by ASH in 2018 to foster collaborative partnerships that accelerate progress in hematology, with the goal of improving the lives of people affected by blood diseases. As a major initiative within ASH RC, the Data Hub aims to create the largest shared information resource within the global hematology community. ASH RC also contains a SCD Clinical Trials Network (SCD CTN), an ambitious project designed to accelerate the development and evaluation of therapies in a large proportion of the United States population affected by SCD. Through the Data Hub, SCD CTN, and projects still to come, the ASH RC will transform research and practice in malignant and nonmalignant hematologic diseases throughout the world, for the benefit of patients and the hematology community.

**Growing the Data Hub**

The Data Hub is open for data contributions toward two initial diseases, multiple myeloma (MM) and SCD. We have already integrated a critical mass of data in these diseases that will allow the research community to answer questions of scientific interest. To date, the Data Hub has integrated data from six academic centers throughout the United States and Europe, representing thousands of patients with MM and SCD. We anticipate that this data repository will grow exponentially in 2020. The Data Hub also recently announced the contribution of the ASPIRE and ENDEAVOR data sets from Amgen, representing more than 1,300 patients with MM on therapeutic clinical trials, and the FISCO registry data set from Novartis, representing observational data from 500 patients with SCD.

In 2020, as the SCD CTN is launched, the plan is for data from patients with SCD at all participating CTN sites to be incorporated into the Data Hub. These data will represent consecutive patients with SCD who are seen at these sites—not limited to those on clinical trials—and will include a significant proportion of the U.S. population with this disease. Though MM does not have a CTN within the ASH RC, we plan for a major expansion of U.S. sites contributing prospective MM data to the Data Hub in 2020.

**Reframing Our Data Models**

For data within the Data Hub to inform research and practice, data must be high quality and fit for purpose. We ensure this through the development of disease-specific data models for SCD, MM, and others yet to come. Once initial disease-specific models are developed and published, we will iteratively refine, refine, and update new releases of these models over time.

As we use the term, a “data model” refers to a collection of attributes that explain how we identify, categorize, and make data available for use. Data models contain high-priority data elements for each disease through a process that recognizes that some elements are critical for research and practice, while not all elements can be collected for each patient every time. Data elements have specific definitions, structure, sourcing, frequency, and context of collection. We house our data within a standardized architecture but can acquire and integrate data through a variety of channels. Our data models represent the “targets” to which sites aim their data contributions, while we work with sites to make data available for use. Data models contain high-priority data elements for each disease through a process that recognizes that some elements are critical for research and practice, while not all elements can be collected for each patient every time. Data elements have specific definitions, structure, sourcing, frequency, and context of collection. We house our data within a standardized architecture but can acquire and integrate data through a variety of channels. We also ensure that previously collected data are transformed over time.

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**Diffusion**

Recurrent genetic abnormalities in acute myeloid leukemia (AML) confer distinct clinicopathologic characteristics and are the foundation of modern AML subclassification systems. Among the most common recurrent genetic driver mutations in AML are activating internal tandem duplications (ITDs) at the juxtamembrane domain of the type 3 receptor tyrosine kinase FLT3 (FLT3-ITD) and exon 12 frameshift mutations in nucleosomino-1 (NPM1).1,2,3-ITDs are present in 25 percent of all AML cases and are also found in a subset of acute lymphoblastic leukemia (ALL), whereas NPM1 mutations are more restricted to AML and occur in 35 percent of cases. NPM1-mutated AML is generally associated with a favorable prognosis, while the presence of a FLT3-ITD generally confers a poor prognosis, especially at a high level (>0.5) FLT3-ITD allele fraction.

Although the molecular events underlying the formation of NPM1 mutations and FLT3-ITDs are poorly understood, DNA polymerase slippage near repetitive (microhomology) sequences has long been speculated as a culprit for FLT3-ITDs.1 A study published recently by Dr. Julian Borrow and colleagues analyzed 300 microhomology nor filler.6 Unexpectedly, microhomology was not observed in a majority (62%) of ITDs. In fact, 38 percent of all ITDs contained an additional sequence of unknown origin (nontemplated “filler”) with the remaining 24 percent containing neither overt microhomology nor filler.

To explain the frequent presence of filler in FLT3-ITDs, the authors use a series of mathematical deductions and inferences to suggest an unusual mechanism: activity in the myeloid cells of terminal deoxynucleotidyl transferase (TdT), the DNA polymerase responsible for untemplated additions of nucleotides to V, D, and J exons during the rearrangement of myeloid cells of terminal deoxynucleotidyl transferase (TdT). The researchers hypothesized that if this mechanism were responsible for ITD formation, the sequences immediately flanking the 3′ and 5′ ends of the duplication would include short (1-6 base pairs), homologous sequences (microhomology), which is indeed seen in a minority of cases (Figure 1A compared to 1B).6 Unexpectedly, microhomology was not observed in a majority (62%) of ITDs. In fact, 38 percent of all ITDs contained an additional sequence of unknown origin (nontemplated “filler”) with the remaining 24 percent containing neither overt microhomology nor filler.

Although canonical thought of as restricted in expression to lymphoid cells, TdT is also known to be expressed in a subset of AML at diagnosis and in myeloid progenitors. Supporting the involvement of TdT in the myeloid cells of terminal deoxynucleotidyl transferase (TdT), the DNA polymerase responsible for untemplated additions of nucleotides to V, D, and J exons during immunoglobulin and T-cell receptor rearrangement. Although canonical thought of as restricted in expression to lymphoid cells, TdT is also known to be expressed in a subset of AML at diagnosis and in myeloid progenitors. Supporting the involvement of TdT in the myeloid cells of terminal deoxynucleotidyl transferase (TdT), the DNA polymerase responsible for untemplated additions of nucleotides to V, D, and J exons during immunoglobulin and T-cell receptor rearrangement.

Recurrence of FLT3-ITDs was also observed in a subset of human hematological malignancies. Studies have also shown that the presence of FLT3-ITDs is associated with a less favorable prognosis.8,9 In addition, the presence of FLT3-ITDs has been shown to be predictive of response to therapy and overall survival.8,9 In the context of this case report, the presence of FLT3-ITDs was associated with a poor prognosis and may have implications for treatment decisions.
President’s Column

Improving the Poor Prognosis of Grant Applications

During the Fall of 2018 I was getting really worried. Despite submitting numerous grant applications, nothing was being funded, and I could glimpse the need to winnow down my research staff in the not-too-distant future. I was already making some shifts to conserve funds, much as a cell goes into starvation mode and shifts its metabolism, to try to survive until times got better. And then I received a couple of email notices telling me that grants had been funded. Just like that, I went from the depths of despair into the sweet light of a few more years of guaranteed funding. But it was a powerful reminder about what it would feel like to not have research funding. I know many colleagues who are facing the same unpleasant situation right now, and with a poor prognosis for any particular grant application, there’s little I can honestly say that’s reassuring.

The National Cancer Institute just announced that their 2020 funding level for R01s will increase from the 8th percentile to 16th percentile for new grants and competitive renewals and to the 16th percentile for early-stage investigators. The National Heart Lung and Blood Institute’s 2020 funding pay lines are at the 16th percentile for R01 grants and the 26th percentile for early-stage investigators. While other Institutes have not yet released their numbers, the numbers we do know are better than those in recent years; but most National Institutes of Health (NIH) applications still will not be funded. Given the effort it takes to write an NIH application, these success rates are extremely discouraging. ASH is continuing its Bridge Grant program for investigators who are revising and resubmitting NIH grants, to try to retain hematology investigators. ASH has distributed more than $17 million through the program since its inception, with more than 70 percent of the recipients subsequently being awarded an R01 from NIH within three years. Foundations and other funding sources such as the Patient-Centered Outcomes Research Institute (PCORI) continue to support research but are also highly competitive. While we should celebrate the recent consistent increases in the NIH budget, the reality is that we are still below the buying power of 2003, and the drought from 2003 to 2015 (Figure) has probably forced many people to leave research and discouraged others from even trying to pursue a research career. I don’t have any hard data to back up my assertions; I’m just reporting the anxious pulse I feel of fellows and faculty who don’t see a path to enter or remain in academic research.

This issue of The Hematologist is filled with articles describing advances in our understanding of hematology and improvements in care, built upon solid basic and clinical research conducted by hematologists. ASH continues to lobby for consistent and robust research funding to keep the pipeline of breakthroughs gushing. If it takes years or decades for research to reach the prescription pad and for young investigators to reach their peak of productivity, then the effects of a 12-year dry spell may not be felt for another decade. It is important that legislators and the public be reminded that their investment in research is long-term, but the payoffs are potentially huge. So if you are conducting funded research and giving a presentation or an interview, please make sure that you not only thank your funding sources (e.g., “I’d like to thank my funding sources for their support”) but that you explicitly tell your audience, “…without which, this work would not have been possible.”

Stephanie J. Lee, MD, MPH
The Hematologist Board of Contributing Editors Welcomes Three New Additions in 2020

The spring season reminds us of the many transitions all around, and this certainly applies to The Hematologist. In December 2019 in Orlando, I shared ASH’s deep gratitude to three outgoing Contributing Editors: Drs. Caron Jacobson, Lori-Ann Linkins, and Stephan Moll.

Dr. Jacobson, of the Dana-Farber Cancer Institute, used her expertise and insight to explain novel treatments for lymphomas and the latest data on CAR T-cell therapy at a time when application of this therapy was rapidly expanding. Dr. Linkins, whose home base is McMaster University, contributed a wealth of knowledge in the research of deep vein thrombosis, bleeding disorders, and much more. Lastly Dr. Stephan Moll was our resident expert in the area of hemostasis and thrombosis. Not only will we miss his in-depth reviews on therapeutic advancements, but Dr. Moll’s willingness to report on unique professional opportunities (such as being called to consult on a lemur with a possible vascular event) lent humor and variety to our publication.

Without a doubt, each of these experts has made a positive impact on the mission of The Hematologist. One of the great joys of this work is being able to interact with so many varied professionals and to learn from their work, expertise, and experience, and I have passed on the thanks of ASH and our readership to each of these individuals.

This publication could not happen without the dedication and commitment of our Contributing Editors. Of course, with each farewell, there is always a welcome, and we are thrilled that the ASH Executive Committee approved the nominations of three new Contributing Editors — Drs. Damon Houghton, Frederick Locke, and Eric Tseng.

— Laura C. Michaelis, MD

Dr. Damon Houghton is assistant professor of medicine in the Department of Cardiovascular Disease, Division of Vascular Medicine, and the Department of Internal Medicine, Division of Hematology/Oncology, at the Mayo Clinic in Rochester, Minnesota. He is a specialist with training in hematology and vascular medicine, and his primary research interest involves optimizing the care of patients with, or at risk for, venous thrombosis. His clinical practice consists of a hybrid of thrombophilia, coagulation, and vascular medicine.

Dr. Frederick Locke is vice chair and associate member of the Department of Blood and Marrow Transplant and Cellular Immunotherapy, and co-leader of the Immunology Program at Moffitt Cancer Center. His clinical and translational research is focused on cellular therapies for lymphoid malignancies. He is lead investigator for several multicenter CD19 chimeric antigen receptor T cell trials, and his lab evaluates immune responses in the context of cellular therapies.

Dr. Eric Tseng is a hematologist in the Division of Hematology/Oncology at St. Michael’s Hospital and assistant professor at the University of Toronto. His practice focuses on nonmalignant hematology and thromboembolism. Dr. Tseng completed adult hematology training at the University of Toronto and a thromboembolism fellowship at McMaster University. He is involved in knowledge translation activities through ASH and Thrombosis Canada. His academic interests include quality improvement initiatives related to the diagnosis and prevention of venous thromboembolism and the implementation and evaluation of hematology training programs.

New ASH Clinical Practice Guideline on Sickle Cell Disease Now Available

The Society has released a new ASH Clinical Practice Guideline on Sickle Cell Disease (SCD). The ASH Clinical Practice Guideline on SCD-Related Transfusion Support is part of a series of five SCD guidelines ASH is developing to provide updated treatment guidelines that reflect the newest evidence about the disease to help the medical community better treat people with SCD.

You can access the full guidelines on the Blood Advances website (www.ashpublications.org/bloodadvances/article/4/2/427/440607). For additional information on other ASH Clinical Practice Guidelines, visit www.hematology.org/guidelines.

ASH and The Leukemia & Lymphoma Society Team Up to Connect Patients With Blood Cancers to Clinical Trials

ASH and The Leukemia & Lymphoma Society (LLS) Clinical Trial Support Center (CTSC) are collaborating to expand access to LLS’s unique free service providing clinical trials navigation and support to patients with blood cancer and their families. With only 5 to 8 percent of adult cancer patients enrolling onto clinical trials, this collaboration aims to bridge this gap and connect more patients to appropriate clinical trials. Through this collaboration, ASH member physicians and their care teams, along with patients and caregivers, receive one-on-one support from CTSC Nurse Navigators and have direct access to them for the duration of the search, enrollment process, and while patients are on the trials.

In a new podcast from The Hematologist (available on SoundCloud and iTunes), Dr. Gwen Nichols from LLS and Dr. Jennifer Holter-Chakrabarty of the ASH Task Force on Immunotherapy discuss this great new collaboration and explain how to use the portal. Visit www.hematology.org/TheHematologist/Multimedia to listen.

The ASH Portal to access the CTSC Nurse Navigators is now live, and you can access it by visiting www.hematology.org/ClinicalTrialNavigation.
Fertility Preservation for Women With Hematologic Malignancies

ALISON W. LOREN, MD, MSCE
Associate Professor of Medicine; Vice Chair, Faculty Development, Department of Medicine; Director, Blood & Marrow Transplant, Cell Therapy & Transplant Program, Raymond and Ruth Schwartz School of Medicine, University of Pennsylvania, Philadelphia, PA

THE CASES

CASE 1: A 24-year-old woman presents with cervical lymphadenopathy and night sweats. An excisional lymph node biopsy confirms classical Hodgkin lymphoma. Positron emission/computed tomography imaging and laboratory testing indicate stage IIB disease with an International Prognostic Index score of 4. Her hematologist is recommending escalated-dose BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone). She is considering fertility preservation and she feels well.

CASE 2: A 30-year-old woman reports blurriness on presentation and further evaluation is found to have splenomegaly (8 cm below the left costal margin), leukocytosis, and anemia (WBC, 25,000/µL; Hgb, 9.9 g/dL; platelets, 289,000/µL). Review of the peripheral blood smear reveals a leukoerythroblastic picture, with all stages of maturation present in the myeloid lineage, and 1 percent blasts on manual differential. Cytogenetic testing demonstrated the presence of t(9;22)(q34;q11). Bone marrow evaluation confirmed chronic-phase chronic myeloid leukemia (CML). Her hematologist recommends initiation of a tyrosine kinase inhibitor. She asks if this treatment will affect her ability to become pregnant, as she was considering pregnancy in the next 12 to 24 months.

CASE 3: A 16-year-old girl is noted to have pallor and reports excessive fatigue. On presentation to her pediatrician, she has leukocytosis, anemia, and thrombocytopenia (WBC, 17,400/µL; Hgb, 8.9 g/dL; platelets, 64,000/µL). A bone marrow biopsy demonstrates precursor B-cell acute lymphoblastic leukemia (ALL). Cytogenetic and molecular studies are normal, and her cerebrospinal fluid demonstrates no evidence of leukemia. Her hematologist is planning to initiate therapy on a pediatric ALL clinical trial with a typical backbone of vincristine, procarbazine, prednisone. She is interested in fertility preservation in the future if her childbearing is delayed.

CASE 4: A 28-year-old woman has noted progressive shortness of breath and bruising. She was planning to discuss these symptoms with her primary care physician, but she developed a fever to 103°F and felt unwell, so she presented for urgent care for evaluation. On examination, she is pale and tachycardic with hypoxemia (oxygen saturation 91% on room air), swollen gums, and numerous ecchymoses. Laboratory data include WBC, 13,500/µL; platelets, 18,000/µL. Immature cells are noted on the differential, and she is transferred to the emergency department of the nearby hospital, where additional evaluation confirmed the presence of 86 percent blasts in the peripheral blood. Bone marrow testing reveals a diagnosis of acute myeloid leukemia (AML; not otherwise specified; with monoblastic differentiation, French-American-British subtype M5a).

THE RESPONSES

Hematologists should address with all patients the possibility of reproductive harm associated with treatments for blood cancer.1-3 Standard-of-care options for preserving fertility in women include oocyte or embryo cryopreservation.4,5 Experimental options such as ovarian tissue cryopreservation4 or ovarian in vitro maturation6 are appropriate in some scenarios; ovarian tissue cryopreservation is currently the only option available to pubertal girls.

Pursuit of oocyte or embryo cryopreservation requires a period of 10 to 14 days of hormonal ovarian stimulation, followed by oocyte retrieval via a transvaginal approach.6,8,14,15 Hence, patients must be clinically stable enough to delay cancer-directed therapy. The decision is a personal one for the patient. While embryo cryopreservation is associated with slightly higher live birth rates, this procedure requires a male partner (or willingness to use donor sperm) and no ethical objections to the freezing and storing of embryonic tissue. Hence, for some women, oocyte preservation may be preferable.

CASE 1: This patient is anticipated to receive high-dose alkylator-based therapy, which carries a high risk of permanent infertility and is certainly associated with premature ovarian insufficiency (POI), a condition defined as cessation of menstrual periods due to ovarian failure at a young age, typically under the age of 40.17-19 She is otherwise clinically well. There is little to no harm in delaying her chemotherapy for approximately two weeks. She should be referred urgently to gynecology/reproductive endocrinology for consideration of oocyte (or embryo) cryopreservation. In this circumstance, facilitated referrals are essential for the best care of the patient.

Hematologists should cultivate relationships with their colleagues in reproductive endocrinology through educational opportunities such as grand rounds, multidisciplinary conferences) and other collaborations; dedicated referral lines and social workers or patient navigators can be indispensable in securing expedited appointments.17,19

CASE 2: Tyrosine kinase inhibitors (TKI) are U.S. Food and Drug Administration pregnancy category D drugs. Hence, this young woman has a few options to consider: 1) initiate therapy with a high-potency TKI (e.g., nilotinib) with hope of achieving a rapid molecular response, then holding the TKI while attempting to conceive, and resuming TKI after delivery (assuming she has not met criteria for treatment-free remission); 2) refer oocytes now (or during TKI therapy) and plan for pregnancy using a gestational carrier; or 3) attempt pregnancy now, prior to initiating therapy, with very close hematologic monitoring and consideration of interferon alfa if needed.20

CASE 3: Typical ALL regimens, particularly pediatric protocols, carry little risk of inducing permanent amenorrhea;4 risk of premature ovarian insufficiency is less well described. This young woman should be counseled about the small risk of reproductive harm, but probably does not require specific fertility interventions. After treatment is completed, she should be referred to gynecology for fertility assessment and counseled about the possibility of POI. She may consider cryopreservation of oocytes in the future if her childbearing is delayed.

CASE 4: This patient is critically ill with disseminated intravascular coagulation, leukostasis, and likely sepsis. It is not appropriate to delay her therapy; on the contrary, emergency interventions are required to manage her AML.19,22 She should be counseled about fertility risks with AML therapy, which is infrequently associated with permanent amenorrhea.19 Consideration should be given to administering a gonadotropin-releasing hormone antagonist (GnRHa) such as leuprolide to achieve menstrual suppression prior to induction. A GnRHa may also induce some measure of ovarian protection, and while data are scant, a GnRHa is unlikely to cause harm in this regard.21,22 Although ovarian tissue cryopreservation may be done immediately as experimental therapy, this technique is contraindicated in patients with acute leukemia owing to the concern of transmitting leukemic cells back to the bone marrow. Hence, patients must be clinically stable enough to delay cancer-directed therapy. The decision is a personal one for the patient. While embryo cryopreservation is associated with slightly higher live birth rates, this procedure requires a male partner (or willingness to use donor sperm) and no ethical objections to the freezing and storing of embryonic tissue. Hence, for some women, oocyte preservation may be preferable.

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Fertility preservation approach for women (postpuberty) with newly diagnosed hematologic malignancy.

Reprinted from Loren et al. Blood. 2019;134:746-780.
For Some Hematologists, Advocacy Takes On a More Personal Meaning

All hematologists advocate on behalf of their patients, but for some doctors who are patients themselves, advocacy is personal. The Hematologist recently spoke with Dr. Kyle Davis, an ASH member who was born with hemophilia A and has been a lifelong advocate for patients with special health care needs. Now in his third year of a pediatric hematology/oncology/bone marrow transplantation fellowship at Nationwide Children’s Hospital in Columbus, Ohio, Dr. Davis is working to improve patient outcomes in children with bleeding disorders and continues to engage in advocacy work through the ASH Grassroots Network.

Dr. Davis’ first introduction to patient advocacy came through his involvement with the Columbus chapter of the National Hemophilia Foundation. Before he was a physician, he visited state policymakers in Ohio and congressional staff in Washington, DC, as part of advocacy days organized by the National Hemophilia Foundation and the Ohio Bleeding Disorder Council.

Dr. Davis saw firsthand the difference he could make through advocacy when Ohio proposed to reduce funding for the Bureau for Children with Medical Handicaps (BCMH) program, which supports families with specialized health care needs in Ohio. “My proudest advocacy achievement was working with the Ohio Bleeding Disorder Council and Rep. John Patrick Carney to protect the BCMH program,” he said. “My testimony and our introduction of a bill with Rep. Carney helped maintain funding for our families.”

Dr. Davis acknowledges that legislative victories like this do not happen in a vacuum, and he recognized the need for organizations such as ASH to mobilize as many advocates as possible to explain to legislators why certain issues matter. Now that he is a practicing hematologist, Dr. Davis has joined the ASH Grassroots Network, which provides members with regular updates and information about how to stay in touch with members of Congress.

The Society can also help arrange meetings for Grassroots Network members with their legislators, either in Washington, DC, back home, and provide fact sheets and talking points to use in these meetings.

With the support of the ASH Grassroots Network, Dr. Davis has worked hard to build good relationships with his elected officials at both the state and federal levels. Keeping regular correspondence with your elected members of Congress helps to establish you as a known resource for your legislator’s office and provides a way to continually educate lawmakers on how they both impact hematology practitioners and patients. “I recognize that legislators are motivated to care for their constituents but often do not know how their work will directly impact our ability to care for our patients,” explained Dr. Davis. “We stand in a very important position to provide that insight and offer personal stories about how their decisions affect our patients’ lives.”

In addition to being a member of the Grassroots Network, Dr. Davis expanded his role in the Society’s advocacy efforts last year by participating in the ASH Advocacy Leadership Institute (ALI), a two-day program in Washington, DC, that teaches ASH members to be effective hematology advocates. “By participating in ALI, I have been introduced to many strong advocates within my own state as well as the hematology community,” Dr. Davis explained.

ALI participants undergo in-depth training on ways to be effective advocates on behalf of hematology, regardless of previous experience. The program begins with learning about the federal legislative process and health policy as well as training for effective ways to influence the U.S. Congress. The program ends with participants visiting their congressional delegation on Capitol Hill to apply what was learned. “The most important take-home message for me was regarding how to make your senators or representatives understand the importance of your request by telling them a story to help explain how they could help our patients,” said Dr. Davis.

ASH is dedicated to supporting its members in advocating for hematology at the local, state, and national levels of government. To learn more and sign up for the ASH Grassroots Network, visit the ASH Advocacy Center (www hämatology.org/Advocacy).

Additionally, nominations are now being accepted through May 31, 2020, for the 10th annual ALI, which will be held in Washington, D.C., on September 22-23, 2020. More information on ALI and ASH/ALI can be found at www.hematology.org/ALI.

2019 Advocacy Highlights

Hematology advocates from across the country helped lead a very successful year of advocacy for the Society in 2019. ASH attended more than 150 meetings with congressional offices and sent nearly 1,500 letters to Congress on a variety of issues from protecting access to care for patients, to supporting medical research funding. If you would like to be involved in a future advocacy campaign either at the state or federal level, reach out to ASH Government Relations Coordinator, Foster Curry at fcurry@hematology.org.
Precision Medicine in Clonal Hematopoiesis: New Data on Risk for Transformation

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Editor’s Note: The first mention of clonal hematopoiesis (CH) of indeterminate potential as a named entity appeared in PubMed in 2015. Since then, this condition has been the subject of numerous, critically important investigations. In this Mini Review, Drs. O’Sullivan and Mead highlight two recent publications that expand what we know about the relationship between CH and the development of outright hematologic malignancies.

CH is a well-recognized entity where a somatic mutation is acquired by a single hematopoietic stem cell, confers a fitness advantage, and leads to clonal expansion. Eventually, the hematopoietic stem cell-derived clone expands such that it contributes to a considerable proportion of mature blood cell production in apparently healthy individuals. CH is more prevalent with increasing age and carries an increased risk of later evolution to a myeloid neoplasm (MN). Mutations most often detected in CH mirror those seen in overt MNS; these include epigenetic modifying genes (DNMT3A, TET2, ASXL1, IDH1/2), splicing factors (SF3B1, SRSF2, U2AF1), and DNA damage response (DDR) pathways (TP53, CHEK2, and PPMD1). MN-associated signaling pathway mutations are less frequent in CH, except for the JAK2 V617F mutation. Numerous studies have helped to refine the risks of transformation in CH, and a crucial role for mutations affecting DDR pathways is emerging. Several important studies have described that TP53 or PPMD1 mutation–associated CH is particular after previous cancer treatment. Furthermore, MNs arising after chemotherapy or radiotherapy (therapy-MNs [tMNs]) are also enriched for TP53 and PPMD1 mutations, which are often present prior to cancer treatment.

TP53, a tumor suppressor gene, is the most commonly mutated gene across all cancers and in MNs is associated with very poor outcomes and resistance to standard treatments. When present in patients with tMNs, TP53 mutation is associated with a similarly dismal prognosis. Therefore, new approaches for early detection and prevention of TP53-associated MN are badly needed. However, not all patients with TP53 mutation develop tMNs. So how do we identify patients who might be at particular risk of tMNs through cell-intrinsic or cell-extrinsic factors? Regarding cell-intrinsic factors, a wide spectrum of different TP53 mutations can occur as mono- or biallelic mutations. Whether such TP53 mutation allele imbalance has important clinical implications remains unclear, as monoallelic TP53 mutation can mimic TP53 loss of function by exerting a dominant negative effect.

Hoping to shed light on this question, Dr. Elsa Bernard and colleagues recently reported an analysis of TP53 mutations in myelodysplasia (MDs) patients (n=3,324), inclusive of a subgroup with therapy-related MDS (n=229). They studied the TP53 allelic state using a combination of conventional G-banding analyses and a next-generation sequencing (NGS) panel covering TP53 and genomewide copy number probes. One-third of TP53 mutant cases of MDS were monoallelic and two-thirds had multiple hits, consistent with biallelic mutation. Variant allele frequency (VAF) measurements for most cases correlated with monoallelic or biallelic states. However, some patients with VAF below 50 percent (n=19,378 patients) had copy neutral loss of heterozygosity at the TP53 locus and would have been miscategorized as monoallelic if based on VAF alone. Therefore, VAF should not be used as the sole method of assigning allelic state.

Biallelic TP53 mutations were associated with poorer survival and an increased risk of acute myeloid leukemia (AML) transformation in contrast to persons with monoallelic TP53 mutation where the outcome was comparable to that of TP53 wild-type patients. Serial sample analysis in patients with AML transformation detected a higher proportion of biallelic TP53 alteration at the time of transformation, underlining the key role for loss of wild-type TP53 as the event that drives disease progression. Previous studies have also reported better survival in MDS patients with TP53 mutation with VAF below 20 percent (monoallelic for the majority). However, analyses in AML found TP53 mutations to be associated with adverse prognosis irrespective of VAF.

Patients with tMNs in this study had a higher frequency of multiple mutations of TP53 as compared with de novo cases (64% vs. 65%; OR, 2.8; p=0.002). The same observations for clinical outcomes were made in this tMN subgroup; those with biallelic mutations had poorer outcomes compared to those with monoallelic TP53 mutations who had a lower risk of death, though this did not achieve statistical significance.

The relationship between CH associated with DDR mutations, chemotherapy treatment, and risk of IMN was studied in greater depth by Dr. Kelly Bolton and colleagues. Their group set out to determine novel approaches that might be used for early intervention and targeted prevention for patients with cancer at high risk of developing tMN. They analyzed targeted, deep coverage NGS data (MSK-IMPACT) to detect CH in a very large cohort of patients with cancer (n=24,439). Strikingly, the authors reported a prevalence of CH mutations in almost one-third of patients. More than half of the mutations detected were classified as putative driver mutations of cancer, and virtually all affected genes recurrently mutated in MNs. Reflecting prior studies, the most commonly identified CH mutations affected epigenetic modifier genes DNMT3A and TET2, as well as DDR genes TP53, CHEK2, and PPMD1. Correlation between CH and clinical characteristics was performed for 10,207 patients; 61 percent had exposure to cancer therapy prior to CH analysis, and 39 percent were treatment naïve. The authors found that CH was associated with increasing age (OR, 1.8; p=0.01) and cell intrinsic factors such as smoking exposure (OR, 1.1; p=4.1 × 10^-9) and previous exposure to cancer therapy (OR, 1.2; p=4.2 × 10^-7). Although splicing factor mutations were less commonly detected, they were more strongly correlated with older age. TP53 (OR, 2.7; q=9.0 × 10^-8), PPMD1 (OR, 3.6; q=1.2 × 10^-6), and CHEK2 (OR=4.9, q=1.0) mutations were significantly associated with previous exposure to cancer therapy, an association not seen for mutations in epigenetic modifiers or splicing factors. CH was most strongly associated with topoisomerase II inhibitors (OR, 1.3; p=0.01) and platinum drugs (OR, 1.2; p=0.01) — carboplatin specifically (OR, 1.3; p=0.002) — for the latter class. Consistent with these observations, carboplatin is particularly associated with risk of tMN. A dose-response relationship was observed between cancer therapy and the prevalence of CH; a higher cumulative exposure to external beam radiation and platinum chemotherapies was positively associated with the presence of CH. Specifically for TP53 mutations, significant associations were found in patients with exposure to platinum, taxanes, and radiation therapy.

Serial analysis in 325 patients allowed interrogation of the clonal dynamics of CH after cancer therapy. Sixty-two percent of persons with a CH mutation at both time points had a stable allele frequency, whereas in 28 percent of cases, mutations increased in VAF, and 10 percent showed a decrease in clone size. In patients receiving radiation or cytotoxic therapy, there was a selective increase in DDR mutations; moreover, increasing exposure to either (Cont. on page 14)
As many hematology/oncology trainees will learn during their fellowship, certain germline mutations give rise to hematologic disorders. Some of these relationships are seemingly simple—a single base pair alteration leads to a lethal or benign switch in the β5-globin gene, for example. But others are more complex, including the germline mutations that confer leukemic risk or diseases of the megakaryocytes or platelets. There is a growing understanding that to ensure that genetic diagnoses are accurate and patient-centered, the scientific and clinical communities require a solid interpretive infrastructure to safeguard the many stakeholders of these data: What are the true genetic and phenotypic associations? Are all variants equally pathogenic? Are all tests performed in a valid manner? Are the findings actionable?

This is the mission of the National Institutes of Health (NIH) Clinical Genome Resource (ClinGen), a federally funded project aimed at building shared knowledge repositories for genes and their variants. In early 2018, ASH partnered with the University of North Carolina (UNC) at Chapel Hill, an NIH ClinGen grantee, to develop a broad and accessible collection of genomic data aimed at improving the diagnosis of myeloid malignancies and hereditary platelet disorders. The two expert review panels have been working for nearly two years on this and have begun publishing their findings.1 Drs. Lucy Godley (Section of Hematology/Oncology and Center for Clinical Cancer Genetics, The University of Chicago, Chicago, IL) and David Godley (Section of Hematology/Oncology and Center for Clinical Cancer Genetics Department of Laboratory Medicine, University of Washington, Seattle, WA) co-lead the panel developing curation rules for variants in genes that confer risk for hereditary myeloid malignancies, and Drs. Jorge Di Paola (Department of Pediatric Hematology and Oncology, University of Washington, Seattle, WA) and Wolfgang Bergmeier (Section of Hematology/Oncology and Center for Clinical Cancer Genetics Department of Laboratory Medicine, University of Washington, Seattle, WA) co-lead the panel for platelet disorders.

Michaelis: It seems like the impact of variants might be different if one were focusing on different tissues. I take it that your two panels are, for now, specifically interested in the bone marrow or megakaryocyte lineage?

Godley: Exactly right. Yes, we are classifying variants that are conferring risk to the bone marrow to develop myeloid malignancies. We started with RUNX1 because it had the greatest number of variants in publicly available ClinVar, which is where the variant data are first deposited. And we also thought it would be helpful, since RUNX1 mutation carriers also have thrombocytopenia and the other ASH-sponsored ClinGen committee is working on germline predisposition to thrombocytopenia. So we thought that would be a nice starting place. It took us about a year-and-a-half to generate these rules for RUNX1. It’s quite a rigorous process I have to say, and it’s been really interesting and eye-opening.

Di Paola: Our group opted to start with probably the most well-known platelet disease on earth—Glanzmann thrombasthenia, first described by the Swiss pediatrician Eduard Glanzmann in 1918, where there is an absence or deficiency in the platelet fibrinogen receptor (GPIIb/IIIa). This receptor is encoded by two different genes: ITGA2B and ITGB3. The reason we started with that is that this disease has been genetically well characterized all over the world. We said, “we have a lot of biological information, we have a lot of publications, we have a lot of genetic data that have already been published, and we have databases on these genes.”

Michaelis: Initial publications from your panels are out or pending, correct?

Godley: Yes, a paper discussing our detailed curation rules is now published in Blood Advances.1 For the most part, I think the end users of our Blood Advances paper are the clinical laboratories that are generating the variant interpretation. So now when a clinical laboratory sees a RUNX1 variant, it will be able to use these rules to say whether this variant is known pathogenic, likely pathogenic, variant of unknown significance, likely benign, or benign—five different levels of functional annotation. The variants that are in ClinVar are already being classified by our committee using those rules, so that if a clinical laboratory sees a variant, they’ll first go to the ClinGen/ClinVar website and see whether this variant has been classified already by the committee. Any variant that’s already deposited has essentially been classified by the rules, and that makes their job very easy. If they have a new variant that’s never been described, then they’ll use these rules to classify it. If you see the

Michaelis: Which genes or disorders will you tackle next?

Godley: We’ve started with RUNX1, and we’re working on curation rules for GATA2 right now. After that, we probably need to do DDX41, CEBPA, [and] ETV6. Although ETV6 could be shared with the thrombocytopenia committee.

Di Paola: We’re going to curate the most traditional platelet diseases first, such as Bernard-Soulier syndrome caused by defects on the von Willebrand factor receptor, the GPIba-IX-V complex on the platelet surface. After that, we’re going to start to go deeper into other disorders, and probably after we finish what we know about platelet function disorders, we’re going to go into other thrombocytopenias such as those caused by MYH9 mutations.

Michaelis: What do your output mean to patients and, not necessarily geneticists, but the working hematologist?

Godley: The first thing I would say is that we are identifying more and more families and individuals based on molecular profiling of leukemia cells. Because the prognostication of the leukemia is so dependent on understanding the molecular testing, and many of these genes are included in those panels, we are very often finding these individuals and families at the time of diagnosis of the first leukemia in the family. Recognition that molecular profiling of a tumor cell yields both germline and somatic data is extremely important. Labeling these tests as “somatic panels” is extremely misleading. It’s critical to recognize that when you see a TP53, a RUNXI, a DDX41, a CEBPA, or a GATA2 mutation in a myeloid leukemia, you have to question: Is this a germline variant? And once you determine that it’s germline, you now have rules that are quite rigorous in terms of the functionality of that variant.

Di Paola: Most of us dream of platforms that are comprehensive enough that when you get your genetic test back, your doctor or hematologist would be able to check on a website and confirm with other sources and eventually tell you, “This is everything that we know about this variant.”

There is a lot of misinformation out there and a lot of fear. I think that overall if we do our job well, in several years, we’re going to be able to truly diagnose these disorders in a way that the patient will understand if they do have or do not have the disease. And, of course, genetic counselors will be absolutely needed to interpret with patients and families the implications of these findings. The fact that ASH is supporting this is fantastic because it has to happen.

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The MEDALIST Trial: Are We on the Podium for Lower-Risk MDS?

P. Fenaux, U. Platzbecker, G.J. Mufti et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. N Engl J Med 2020;382:140-151.

KRISTEN O’DYWER, MD

The myelodysplastic syndromes (MDS) are a diverse group of malignant hematopoietic stem cell disorders characterized by ineffective hematopoiesis, blood cytopenias, and an increased risk of transformation into acute myeloid leukemia (AML). The revised International Prognostic Scoring System (IPSS-R) is a commonly used clinical prognostic tool that utilizes variables from the blood and marrow to place patients into one of five risk groups, based on risk of mortality and transformation to AML. For patients with “lower-risk” MDS, which comprises the IPSS-R very-low, low, and intermediate-risk groups, the disease is characterized by a low risk of transformation into AML, a relatively prolonged survival, but a high prevalence of anemia. Over time, approximately 40 percent of patients will need frequent red blood cell (RBC) transfusions.

The first-line treatment for transfusion-dependent patients with lower-risk MDS (those without the chromosome abnormality of deletion 5q) are the erythropoiesis-stimulating agents (ESA). For patients who do not respond to or are ineligible to receive ESAs, there are few treatment options for chronic anemia. Accordingly, the identification and translation of novel therapies capable of improving the marrow function in patients with MDS has the potential to significantly improve quality of life and overall outcomes for patients with MDS.

Luspatercept is a novel recombinant fusion protein that consists of a modified extracellular domain of the human activin receptor type IIB (ACR-IIIB) linked to the human immunoglobulin G1Fc domain. It binds to select transforming growth factor-β superfamily ligands and neutralizes them, and consequently inhibits erythropoiesis in the marrow and late-stage erythroblast differentiation. Importantly, the mechanism of action seems to be independent of erythropoietin regulation. In November 2019, the U.S. Food and Drug Administration (FDA) approved luspatercept for the treatment of anemia in adult patients with β-thalassemia who require regular RBC transfusions, and luspatercept is being studied for treatment of MDS-associated anemia.

The safety and efficacy of luspatercept was tested in a single-arm phase II study of 58 patients with lower-risk MDS with anemia. Sixty-three percent of patients demonstrated an erythroid response, and 38 percent were transfusion independent for 8 weeks or longer. Patients with the ring sideroblast phenotype had the optimal responses, however, with 69 percent achieving an erythroid response and 42 percent becoming transfusion independent for 8 weeks or longer. Based on these promising phase II results, a randomized phase III trial (NCT026831070) was initiated to test luspatercept for the treatment of anemia in patients with lower-risk MDS with ringed sideroblasts who were transfusion dependent.

In the current article, Dr. Pierre Fenaux and colleagues report on the prospective, international, multicenter, double-blind, placebo controlled, phase III MEDALIST trial. The trial enrolled 229 patients in 65 trial sites in 11 countries. Eligible patients had lower-risk MDS and were RBC transfusion dependent, defined as receiving at least two or more red blood cell units per eight weeks. In addition, each patient’s anemia had to be classified as refractory to or unresponsive to ESAs, or they had to have discontinued ESAs due to a prior adverse effect. Patients were randomly assigned in a 2:1 ratio to receive luspatercept or placebo, at a dose of 1 mg/kg administered subcutaneously every three weeks for 24 weeks. The dose of luspatercept could be escalated during the treatment to 1.75 mg/kg. The MDS disease assessment was performed at 24 weeks after the start of study treatment and then every 6 months thereafter. The primary endpoint was transfusion independence for 8 weeks or longer during weeks 1 through 24. Important secondary endpoints were transfusion independence greater than 12 weeks during the first 24 weeks and also within the first 48 weeks. Patients were observed for three years following the last dose of study treatment for AML progression and overall survival.

Thirty-eight percent of patients in the luspatercept group achieved the study’s primary endpoint of at least eight weeks without the need for transfusion compared to 13.2 percent in the placebo group (p=0.001). The median duration of transfusion independence was 30.6 weeks in the luspatercept group and 13.6 weeks in the placebo group. For the key secondary endpoint, 28 percent of patients in the luspatercept group achieved red cell transfusion independence for 12 weeks or longer compared to 8 percent in the placebo group. Also, during weeks 1 through 24, an erythroid response was observed in 53 percent of patients in the luspatercept group compared to 12 percent in the placebo group. The adverse events most frequently reported during the luspatercept treatment group were fatigue, diarrhea, anemia, nausea, dizziness, and back pain. The risk of progression to higher risk MDS was low (1 patient in each treatment group), as was the development of AML (2 percent in the luspatercept group and 1 percent in the placebo group) in the three-year study period. Long-term follow-up of the patient cohorts is ongoing, however.

Overall, luspatercept treatment lead to transfusion independence for eight weeks or longer, improved the erythroid response, and was associated with low-grade adverse events in patients with lower-risk MDS. The FDA announcement for luspatercept is expected in April 2020. It is expected that the MEDALIST trial will earn its spot on the FDA’s podium with an approval for luspatercept. The phase III COMMANDS trial (NCT03882536) is evaluating the efficacy of luspatercept versus placebo in patients with and without ring sideroblasts who have not received prior ESA for MDS. This agent represents a promising treatment for chronic anemia in patients with lower-risk MDS.
Testosterone Therapy in Men Doubles the Risk for Venous Thromboembolism

Walker RF, Zakai NA, MacLachone RF, et al. Association of testosterone therapy with risk of venous thromboembolism among men with and without hypogonadism. JAMA Intern Med 2019; doi: 10.1001/jamainternmed.2019.5135. [Epub ahead of print.]

DAMON E. Houghton, MD, MS, AND STEPHAN MOLL, MD

Whether or not testosterone therapy in men increases the risk for venous thromboembolism (VTE) has been a debated topic. Two recent studies have suggested that testosterone therapy may increase the risk for VTE. The Food and Drug Administration’s labeling for testosterone products contains a warning about VTE, yet prior studies on the topic have not been able to reach a definitive conclusion.1-3

Investigators from the University of Minnesota, Dr. Rob Walker and colleagues, performed a case-control study using commercial and Medicare claims data to identify men who had a VTE event. After excluding men without 12 months of continuous enrollment or with a diagnosis of cancer, 39,622 men with VTE were included in the analysis. The authors compared testosterone exposure by drug claims in the six months (case period) prior to the VTE event and six to 12 months (control period) prior to the VTE. Conditional logistic regression with multivariate adjustment was performed to account for hormone-replacement and outpatient emergency department usage in the case and control periods. For the analysis, subjects were stratified into those with a diagnosis code for hypogonadism and those without. In multivariable analysis, hypogonadism (OR, 1.12; 95% CI, 1.02-1.23) use of testosterone within the case period was more frequent than the control period, resulting in an increased odds ratio (OR) ranging from 1.96 to 2.46, with the highest odds ratios found in those with three or more conditions (OR, 2.40; 95% CI, 1.71-3.38). Findings were similar in men with hypogonadism (OR, 1.10), with range from 1.68 to 2.32 and the highest OR at six months (OR, 2.32; 95% CI, 1.97-2.74). In exploratory analyses, the risk remained similar, with testosterone exposure within three months of the VTE event. However, the OR at the three- to six-month case periods were not significant, indicating that men who have taken testosterone for a more prolonged period without developing VTE may have a lower risk.

This study stands out among other research on this topic due to its excellent design and the inclusion of the largest number of VTE cases available for analysis. The case-control design used has been shown to provide a more accurate assessment of risk. The case-control design used here helps eliminate measured and unmeasured confounding, which has been a significant problem with observational studies comparing treated patients to untreated patients, owing to inherent differences in these groups.

The data from this study are consistent with that of another recent observational study, which showed an increased risk for VTE within the first six months after testosterone introduction (RR, 1.63; 95% CI, 1.29-2.3);4 5 6 7 8 9 10 point estimates are also similar to the results of a meta-analysis of the few randomized control trials that had reported VTE outcomes (OR, 1.96; 95% CI, 0.75-5.1).1 9 10

The American College of Physicians recently published a clinical practice guideline7 8 on the efficacy and safety of testosterone treatment in men and noted that the available randomized control trials were not powered to assess important harms. Data from the study by Dr. Walker and colleagues were not included in the observational study, which reviewed evidence as it had not been published at the time of the analysis.

Additional data are being collected. The TRAVERSE study (NCT03518034) is a randomized phase IV study starting in 2018 with an estimated enrollment of 6,000 men with hypogonadism, and will assess long-term major adverse cardiovascular events in men treated with testosterone. Patients with prior VTE are excluded from enrollment. Unfortunately, the information provided on clinicaltrialsgov does not indicate whether the study will specifically evaluate VTE as an outcome, and an inquiry to the study sponsor only led to being referred back to the clinicaltrialsgov website.

Acknowledging that additional randomized controlled trial data may not be available to help us assess the VTE risk with testosterone therapy, this topic is an important and optimally controlled observational study by Dr. Walker and colleagues indicates a short-term doubling of VTE risk with testosterone therapy that should be discussed with all men when considering the risks and benefits of starting testosterone therapy. As always, other VTE risk factors such as age, obesity, smoking status, personal or family history of VTE, and others, should also be considered.

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Identification of Malignant Cell Populations Years Before Development of Treatment-related Leukemia in Patients With Myeloma

Sridharan A, Schinke CD, George G, et al. Stem cell mutations can be detected in myeloma patients years before onset of secondary leukemias. Blood Adv. 2019;3:3962-3967.

AMY E. DeZERN, MD, MHS

Treatment-related myeloid neoplasms (t-MN), including myelodysplastic syndromes (t-MDS) and t-acute myeloid leukemia (t-AML), are a rare but feared complication in patients who previously received chemotherapy and/or radiation for the treatment of a primary cancer; the risk is primary by disease as well as by therapies used.1,2 Multiple myeloma is a chronic hematologic malignancy for which patients, through their lifetime, can receive multiple treatments along with high-dose therapy and autologous hematopoietic stem cell transplantation (aHCT). As such, MDs-associated cyogenetic abnormalities as well as clinical presentations of t-MDS and t-AML have relatively high rates reported in patients with myeloma.3 As these secondary malignancies are most often associated with an unfavorable prognosis, it is valuable to identify risk factors and predispositions that can lead to their development. Information about clonal hematopoiesis of indeterminate potential (CHIP; defined by the presence of somatic mutations in the blood in the absence of cytopenia or overt hematologic malignancy4); which may already present at the time of primary therapy, informs our thoughts about future risk in these patients.5 Additionally, it is important to note where the cell populations that may harbor these mutations may fall in the hematopoietic lineage, as subclones, or in stem or progenitor cells.6

In the current study, Dr. Ashwin Sridharan and colleagues sought to identify whether stem and progenitor cells were the reservoirs of the myeloid mutations that were ultimately seen in the t-MN developing in their patients. Six myeloma patients who developed t-MN after aHCT from a single institution had hemoglobin, identified by CD34 positivity, available from pretransplant harvest. The mean time to t-MN in this small group was five years (range, 3 months to 7.5 years). The group used established and rigorous cell sorting methodology to separately phenotypically normal and abnormal stem cells. Sorted cell populations were used for DNA isolation for targeted sequencing of known genes in t-MN. All six patients had the identical driver mutation (TP53 or RUNX1) observed in the t-MN samples. These mutations were detected in stem or progenitor cells collected at the time of myeloma treatment. The resultant data suggest that aberrant phenotypic leukemia stem cells can be detected years before the clinical onset of t-MN. Unsurprisingly, the stem and progenitor cells likely act as reservoirs of these mutant subclones, harboring the CHIP that ultimately may become the t-MN. Additionally, the authors observed phenotypically aberrant stem cells by CD34 expression of leukemia stem cell markers including CD123 positivity. Previous reports have also demonstrated that CD123+ populations are associated with higher risk of MDS and AML.7

Currently in the field of hematologic/oncology, there is an explosion of data based on our ability to do sophisticated sorting of cell populations as well as next-generation sequencing/molecular testing of peripheral blood and bone marrow in this article. These tests have the ability to detect mutations in individuals without morphologic or cyogenetic evidence of MN. Certainly, t-MN represent a unique clinical scenario in which chemotherapy or radiation may select for a mutant hematopoietic stem cell clone, increasing the risk that this clone will acquire additional mutations and progress to malignancy.8 As shown here in myeloma, similar reports have also shown that individuals with CHIP who are treated for solid tumors have an elevated risk of MN and an increased overall mortality,9 and that mutations in TP53 gain a selective advantage in response to radiation or chemotherapy.10 The ability to identify and characterize the mutation of the patient population to those cells with the leukemia stem cell phenotypes.

Some could make the rational argument that this additional genetic information just “incites panic” in patients and providers alike, without the currently available tools to change therapy for the present disease or a future potential diagnosis. However, much of what we do in hematology/oncology (and medicine globally) is about managing expectations. Increasingly, we are going to have the capacity to sort cells and monitor certain populations to ensure we can make t-MN diagnoses earlier to enable therapeutic strategies in the future. Studies, like the one described here, may also test aberrant CD123 expression on stem cells and whether this presence could be a potential biomarker for future development of t-MN. Therapeutic avenues that target this population may ultimately be feasible.

In summary, the capacity for understanding the biology of t-MN is ever increasing. Our patients will benefit from more widespread and longitudinal follow-up for longitudinal follow-up after initial therapies and further studies will refine these, based on scientific advances. Thereafter, we can look forward to additional therapeutics for our patients.

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5. DLBCL, single-hit
6. DLBCL, double hit with non-IG partner
7. DLBCL, double hit with non-IG partner
8. DLBCL, single-hit MYC recombination with non-IG partner
9. DLBCL, single-hit MYC recombination with non-IG partner
10. DLBCL, single-hit MYC recombination with non-IG partner

Figure

Picking a Partner: As in Life, it Matters for MYC

Rosenwald A, Bens S, Advani R, et al. Prognostic significance of MYC rearrangement and translocation partner in diffuse large-B-cell lymphoma: A study by the Lunenburg Lymphoma Biomarker Consortium. J Clin Oncol. 2019;37:3389-3398.

BRAD KAHL, MD

I have become apparent throughout the past 10 years that “double-hit” diffuse large B cell lymphoma (DLBCL) is a unique entity within DLBCL. It is so unique, that the World Health Organization (WHO) reclassified it in 2016 using the term “high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements.” That’s a mouthful, and in clinic we still just call it “double-hit DLBCL.”

Naming issues aside, what was not in dispute was the universally bad outcomes for these patients when treated with standard R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy. In desperation, treating clinicians have resorted to more intensive strategies such as the dose-adjusted EPOCH-R (etoposide plus R-CHOP) regimen, R-hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, etoposide, and cisplatin) regimen, and an alternating consolidation strategy with high-dose chemotherapy and autologous stem cell transplantation. Retrospective analyses have suggested that outcomes are improved with these approaches but still relatively poor. Additionally, double-hit DLBCL is more common in older patients, who are often not candidates for the more intensive strategies. Therefore, the unmet need is large.

Much work has been devoted to characterizing the biology and natural history of double-hit DLBCL. This entity is defined by the presence of a MYC rearrangement at chromosome 8q24 and a rearrangement in BCL2 at chromosome 18q21 or in BCL6 at chromosome 3q27. If MYC and both BCL2 and BCL6 are rearranged, it has been called “triple-hit” DLBCL. These rearrangements are detected by R-banded chromosome techniques (R-BAND), which are both sensitive and specific for the chromosomal abnormalities they are designed to detect. Of note, the FISH probe commonly used to detect MYC rearrangements is a “break-apart” probe, meaning it detects breakpoints in the MYC loci but does not tell us which gene MYC has partnered with in the DNA rearrangement process. Previous small studies have suggested the partner matters. Specifically, MYC partnered with an immunoglobulin gene (IG) was hypothesized to confer a higher risk outcome than if MYC was partnered with a non-IG gene. A recent large study by Dr. Andreas Rosenwald and colleagues from the Lunenburg Lymphoma Biomarker Consortium has confirmed and refined this observation in a larger cohort of patients.

The investigators had access to more than 2,000 DLBCL biopsy specimens with annotated clinical data. Using the break-apart probe, they found a MYC rearrangement in 264 patients (11% of the patient population). They then further interrogated these cases by using FISH probes for a MYC/IG gene fusion and by using three different FISH probes that could test for IG heavy chain, IG V light chain, and IG light chain. The panel of FISH tests allowed patients to be categorized into one of the following five categories:

1. DLBCL without MYC rearrangement
2. DLBCL, double hit with IG partner
3. DLBCL, double hit with non-IG partner
4. DLBCL, single-hit MYC rearrangement with IG partner
5. DLBCL, single-hit MYC rearrangement with non-IG partner

Kaplan-Meier estimates of (A) progression-free survival (PFS) and (B) overall survival (OS) for patients with diffuse large-B-cell lymphoma without MYC rearrangement (MYC-negative), patients with MYC single hit (SH; immunoglobulin (IG), MYC-SH (non-IG)), MYC double hit/rhizoma (DH/ TH; IG/MYC, DH/TH/MYC), and double hit/triple hit (DH/TTH; IG/MYC, DH/TH/MYC). © Reprinted with permission. Copyright 2019 American Society of Clinical Oncology. All rights reserved. From Rosenwald, A et al: J Clin Oncol 37 (35), 2019: 3359-3368.

The Figure shows the progression-free and overall survival Kaplan-Meier estimates for each of the five groups of patients. The only subgroup with a clear superior outcome compared to the others is DLBCL that is patients with double-hit (or triple-hit) DLBCL with an IG partner for the MYC rearrangement. All other groups experienced outcomes similar to ordinary DLBCL. What are we to make of these findings? The implication is that having double-hit DLBCL is not necessarily worse. Approximately 50 percent of the double-hit patients had no IG partner and outcomes similar to ordinary DLBCL. Should we tell our molecular pathologist to obtain these more specific FISH probes and go the extra mile to characterize double-hit DLBCL cases, before subjecting those patients to intensive strategies they may not need? Possibly. Ideally, these findings will be replicated before we change practice. The absolute numbers of patients in groups two to five were relatively small at 51, 50, 37, and 16 patients, respectively. A larger exploratory analysis of the exact treatment patients received is now needed to verify and validate these results. This is an emerging story, and a clarification is a high priority so that we may optimally risk stratify our patients with DLBCL in the future.

Dr. Kahl indicated no relevant conflicts of interest.
Relapsed acute myeloid leukemia (AML) rapidly evolves into a chemotherapy-resistant disease and is incurable with standard approaches. The genetic factors driving the leukemia also govern chemotherapy resistance and prognosis after treatment. **MLL-rearranged** (MLL1, KMT2A) leukemias are an aggressive clinical subgroup of AML and acute lymphoblastic leukemia (ALL) with poor clinical outcomes, particularly in the context of therapy-associated AML and infant ALL. In the past 10 to 15 years, the molecular pathways governing MLL-rearranged oncogenic transformation have been carefully elucidated, demonstrating the importance of MLL-fusion interactions with chromatin-associated protein complexes. This work has led to the identification of novel drug targets, including DOT1 inhibitors, 1 bromodomain inhibitors, 2 and drugs that interfere with the Menin-MLL interaction. 3 Menin binds to the N-terminus of MLL-fusion proteins and is required for MLL-fusion proteins to regulate aberrant gene expression pathways via the action of DOT1L.

In an exciting recent publication, Dr. Andrei Krivtsov and colleagues used an iterative structure-based design process to identify a highly active inhibitor of the Menin–MLL protein–protein interaction, VTP50469, with a favorable pharmacological profile. The crystal structure confirmed binding within the Menin–MLL binding pocket, and validation in cell lines showed that this compound had antileukemic activity evidenced by reduced cell growth, differentiation, and increased apoptosis. VTP50469 rapidly suppressed the gene expression program in MLL-fusion target genes in various MLL-rearranged cell lines and showed activity at low nM concentrations in AML and ALL. Interestingly, the kinetics underpinning the suppression of gene expression were more rapid than that seen with some other epigenetic therapies such as DOT1L inhibitors. Despite the remarkable efficacy, the effect of VTP50469 seemed to be limited to a discrete subset of MLL-fusion target genes including MEIS1, MEF2C, and JMD1/2C, but not the HOXA cluster. This specificity may have been related to genes with the highest occupancy of Menin and DOT1L binding. It remains unclear why some MLL-fusion target genes are insensitive to the effect of this inhibitor (Figure).

Importantly, this drug was orally bioavailable and showed efficacy in MLL-rearranged murine AML and patient derived xenograft samples from MLL-rearranged AML and ALL. The in vivo effects confirmed the cell culture findings with differentiation of leukemic blasts, on target suppression of aberrant gene expression, and, on prolonged survival. Indeed, some recipient mice appeared to cure, with long-term survival exceeding 450 days. This long-term disease-free survival is rarely seen with monotherapy, or even when combined with chemotherapy. 2 Major dose-limiting toxicities were not observed in this study.

These preclinical results provide optimism but will need to be validated with prospective clinical studies. It is fair to say that there has been only modest efficacy of single-agent chromatin modifying agents such as DOT1L inhibitors 3 and bromodomain inhibitors. 2 It may be that the long-term role of such agents is in combination with chemotherapy, or to eliminate minimal residual disease after treatment. We have come a long way in the past few years with new drugs for leukemia including venetoclax combinations, monoclonal antibodies, and chromatin modifying agents such as DOT1L inhibitors. These exciting preclinical results provide optimism but will need to be validated with prospective clinical studies. The crystal structure confirmed binding within the Menin–MLL binding pocket, and validation in cell lines showed that this compound had antileukemic activity evidenced by reduced cell growth, differentiation, and increased apoptosis. VTP50469 rapidly suppressed the gene expression program in MLL-fusion target genes in various MLL-rearranged cell lines and showed activity at low nM concentrations in AML and ALL. The in vivo effects confirmed the cell culture findings with differentiation of leukemic blasts, on target suppression of aberrant gene expression, and, on prolonged survival. Indeed, some recipient mice appeared to cure, with long-term survival exceeding 450 days. This long-term disease-free survival is rarely seen with monotherapy, or even when combined with chemotherapy. Major dose-limiting toxicities were not observed in this study.

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RENEE SQUIRES, MBBS, AND STEVEN LANE, MBBS, PhD, FRACP, FRCPA

## Outcomes for Children With SR-ALL: More Is Not Always Better

Maloney KW, Devidas M, Wang C, et al. outcome in children with standard-risk b-cell acute lymphoblastic leukemia: Results of Children’s Oncology Group Trial AALL0331. J Clin Oncol. 2019 Dec 11. doi: 10.1200/JCO.19.018106. [Epub ahead of print]

CAROLINE DIORIO, MD, DAVID T. TEACHEY, MD

Dr. Diorio and Dr. Teachey indicated no relevant conflicts of interest.

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3. Sherer AG, Gaynor M, Miller D. Improved disease-free survival of children with acute lymphoblastic leukemia at high risk to receive radiation therapy via bone marrow aspirate on day 8. Blasts were over 5 percent, the patients had a repeat bone marrow aspirate on day 15. Bone marrow response by morphology and minimal residual disease (MRD) were also assessed after induction (day 29). Patients were classified as rapid early responders or slow early responders based on marrow response (Table 1; online only). Patients with MRD greater than 1 percent or an MRD marrow at day 29 were assigned to receive additional weeks of therapy and were also classified as slow early responders if they had MRD less than 1 percent at day 43. Those with M3 marrow at day 29 or who had not achieved a remission (M1) by day 43 were removed from protocol therapy.

Patients with SR-average disease were randomly assigned in a 2×2 factorial design to receive four treatments (Table 2; online only). In addition to the standard consolidation (SC) of vincristine, mitoxantrone, and intrathecal methotrexate, intensified consolidation (IC) included 1 g/m² of cyclophosphamide, an increased number of doses of vincristine, cytarabine, two doses of PEG-ASP, and a lower dose interrupted schedule of mitoxantrone. Initially, patients in the standard interim maintenance arm received oral methotrexate. Augmented interim maintenance included Cytarabine methotrexate and the intensification of PEG-ASP. Augmented consolidation intensity included more doses of vincristine and a second dose of PEG-ASP. Following an amendment in 2008 based on the results of CCG-1991, all patients in the SR-average arm received the more intense chemotherapy, reducing the randomization to between SC and IC only. Patients with SR-high disease were nonrandomly assigned to receive intensified consolidation and two cycles of delayed intensification.

The study enrolled 5,377 patients and included a two-stage consent. Patients initially consented to induction therapy. A second consent was used for postinduction therapy and randomization. A total of 3,992 patients continued on to postinduction therapy; 86 percent of the 1,085 patients who consented to postinduction therapy did so because they or their caregivers refused further protocol therapy. The 6-year event-free survival and overall survival (OS) for all patients were 88.96 percent and 95.54 percent, respectively.

In the SR-average arm, 1,500 patients were randomized between SC and IC. With no difference in induction complete remission rate (CR) between these groups. More recently, COG has redefined SR-average as day 8 peripheral blood MRD less than 1 percent and day 29 MRD less than 0.1 percent. The authors analyzed the difference between the SC and IC arms in the subgroup of patients who would meet this more stringent definition of SR-average and found no benefit of IC over SC. In those patients with day 29 MRD between 0.01 and 0.1 percent, patients had a worse event-free survival and OS compared to outcomes between IC and SC. In all subgroups, IC was associated with significantly higher toxicity, especially infectious toxicities, with an infectious rate of 23 percent in the IC groups and 4.7 percent in the SC group (p<0.0001).

The study enrolled 635 patients on the SR-high arm, and these patients also had excellent outcomes, with OS greater than 90 percent. CR and OS rates in patients on the SR-high arm who were treated nonrandomly with intensified therapy were superior to those patients with low-level MRD who were treated with IC or OS and standard postconsolidation therapy. The 6-year CR rate in the SR-average low-level MRD group overall was 77.46 percent, versus 85.55 percent in the SR-high group.

Historically, intensification of therapy has led to improved outcomes in many patients with ALL. The results of the SR-average arm on AALL0331 demonstrate that for many patients with ALL, further intensification of therapy adds only toxicity without benefit. In contrast, the SR-high patients seemed to benefit from nonrandom intensification of therapy post-consolidation. Thus, there may be some groups of patients that would continue to benefit from nonrandom intensification of therapy. It is becoming increasingly difficult to identify who those patients are. The current generation of COG trials (NCT03914625, NCT03959085, NCT03876769) have changed the paradigm and are testing whether the incorporation of immunotherapies into cytotoxic chemotherapy backbones will improve survival without additional toxicity. Time will tell if this approach will lead to superior outcomes.
Does Renal Function Deteriorate in Individuals With Sickle Cell Trait and Sickle Cell Disease? Now We Know

Olaniran KD, Allegritti AS, Zhao SH, et al. Kidney function decline among black patients with sickle cell trait and sickle cell disease: An observational cohort study. J Am Soc Nephrol. 2020;31:393-404.

The carrier frequency of the sickle gene in African Americans is 8 to 10 percent but can be as high as 20 to 40 percent in some African countries such as Nigeria. This relatively high carrier rate has demanded that we continue to probe its impact on all-cause mortality and morbidity related to end organ function in aging populations and those with chronic illnesses such as hypertension and diabetes, both in the United States and globally. Furthermore, as the population with sickle cell disease (SCD) increasingly survives into adulthood in the United States, chronic kidney disease (CKD) is evolving as a significant and growing public health concern.

To define the trajectory and the rate of decline of estimated glomerular filtration rate (eGFR) in patients with both sickle cell trait (SCT) and SCD compared to the general noncarrier (AA) status among black patients, a group of investigators examined changes in eGFR over a minimum of three time points in 21,800 patients from the Research Patient Data Registry housed in Partners HealthCare (Boston, MA) through a 13 1/2 year period. Among the 10,210 patients eligible for analysis after excluding for missing genotype data and conflicts in coding, the researchers identified 2,210 with SCT, 210 with SCD, and 8,726 who had neither carrier status nor disease as the reference or control group.

In this study, Dr. Kabir Olaniran and colleagues simultaneously evaluated and compared the decline in eGFR among patients with both SCT and SCD, and for the first time, could elucidate “a dose response relationship” between sickle hemoglobin S (HbS) quantitation and eGFR. In comparing the SCT group to controls, they found that SCT was associated with a faster rate of eGFR decline (particularly in male patients) and with associated hyperfiltration at baseline. Their findings suggested that black Americans with SCT lose nearly half an eGFR unit (mL/min/1.73 m²) more of kidney function every year compared to black Americans with AA status. The findings in SCD of accelerated eGFR were both intuitive and counterintuitive.

Other elucidated factors associated with eGFR decline in SCT and SCD were hypertension, diabetes, cardiovascular disease, angiotensin converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs), asprin, statins, and higher leucocyte counts. This was in contrast to a retrospective cohort study that was not designed to tease out the various confounding variables but elicits the question of selection bias. From the indications for hemoglobin electrophoresis in the cohort, they suggest that these patients may be “sicker” than the average black population. The patients were already seeking care and requiring frequent blood analysis, and thus may disproportionately be on aspirin, ACEis, or ARBs. The authors also admit another limitation of their study as the absence of APOL1 status data – a known predictor of CKD in the general population. The potential effects of coinheritance of both SCT and the APOL1 genotype would be important to ascertain, as Dr. Rakhi Naik and colleagues reported recently that the degree of risk of end-stage renal disease was similar in SCT and in those with APOL1 high-risk genotype.

Counterintuitively, in SCT, the authors found an inverse correlation between HbS quantitation and eGFR decline; with a lower HbS being associated with a faster eGFR decline. Could this be because patients with SCT may have lower resting blood pressure? Perhaps a more sensitive indicator of the role of blood pressure in this cohort would be the degree of change from baseline blood pressure rather than the absolute measure.

Hence, while SCT is not itself a “malady,” it is far from benign. To determine all the founders of both increased risk for developing CKD as well as what characteristics are renoprotective, these factors must be incorporated in the design of our next generation of prospective longitudinal cohort studies. This study sheds additional light on the role of HbS on renal function and further strengthens the need to frame the research question and focus the research agenda. 

The authors went on to show how TdT activity could also provide a basis for generation of ITDs in the absence of germline microhomology. In short, TdT added nucleotide runs that, by chance, have homology with nearby 5’ sequence (occult microhomology, Figure, part C) could allow for polymerase repositioning and subsequent duplication. These runs would not be apparent as filler sequence, but they should display the level of G/C bias associated with TdT activity. In a companion study, Dr. Borrow and colleagues extended their analysis sequence approach to 2,450 previously published NPM1 mutations in AML (114 unique mutations), showing that of 114 unique mutations, more than 90 percent of NPM1 mutations, contained filler sequences that were consistent with TdT activity in terms of G/C and dinucleotide bias as well as length distribution (Figure, part D).

FLT3-ITDs and NPM1 Insertions

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Examples of replication showing (A) normal DNA replication, (B) microhomology resulting in mispriming and formation of an internal tandem duplication (ITD), (C) nontemplated addition of nucleotides by TdT and the use of the terminal nucleotide to create an occult single base mispriming event to create an ITD with filler sequence, and (D) a similar occult mispriming event leading to an NPM1 four base pair insertion.

Dr. LaMacchia and Dr. Kim indicated no relevant conflicts of interest.
Patients with traumatic brain injury (TBI) and associated intracranial hemorrhage have high morbidity and mortality. Hematoma expansion after TBI occurs in part due to increased coagulopathy related to hyperfibrinolysis, which occurs through various mechanisms that promote the activation of plasminogen to plasmin and subsequent fibrin degradation. These include the endothelial release of tissue plasminogen activator and activation of protein C.

Transaxamic acid (TXA) is an inhibitor of fibrinolysis, a synthetic lysine analogue that blocks the activation of plasminogen to plasmin. Intravenous TXA has been shown in two randomized trials (>40,000 patients) to reduce death due to bleeding in scenarios driven by hyperfibrinolysis: postpartum hemorrhage (WOMAN) and extracranial bleeding after trauma (CRASH-3). A patient-level meta-analysis of these trials demonstrated that the relative survival benefit of TXA decreased by 10 percent for each 15 minutes of treatment delay, with no benefit after three hours from injury or bleeding onset.1 There was no increase in the risk of seizures or thrombosis with TXA in either study.

The CRASH-3 study investigators examined the efficacy and safety of TXA in TBI. In this large multicenter randomized controlled trial, patients with TBI and reduced Glasgow Coma Scale (GCS of ≤12) or intracranial hemorrhage on computer tomography scan were randomized to receive TXA (1 g IV over 10 hours) or placebo. Patients were initially enrolled within eight hours of injury. However, when the above data on early TXA administration were made available, the protocol was amended to enroll patients within three hours of injury such that 64.4% were enrolled within the 12.7±3.0 hours of the trial analysis. The primary outcome was head-injury-related death within 28 days of injury in patients randomized within three hours. Safety outcomes included seizures and thrombotic events.

Among patients treated within three hours of TBI, the primary outcome occurred in 18.5 percent of the TXA group versus 19.8 percent with placebo (RR, 0.94; 95% CI, 0.86-1.02), which did not reach statistical significance. In a prespecified sensitivity analysis excluding patients with GCS lower than 3 or bilateral unreactive pupils, the results were 12.5 percent with TXA versus 14.0 percent with placebo (RR, 0.89; 95% CI, 0.80-1.00). The effects were not different depending on the severity of head trauma or the presence of other major injuries. Moderate TBI (GCS, 9-15), the primary outcome occurred significantly less frequently with TXA (5.8%) compared with placebo (7.9%; RR, 0.78; 95% CI, 0.64-0.95); there was no significant difference in severe TBI (GCS, 3-8).

In a regression analysis including all 12,737 participants, early (≤3 hours) versus late (>3 hours) TXA administration did not significantly impact on survival at 28 days. However, early treatment with TXA was more effective than later treatment for reducing the primary outcome in patients with mild to moderate TBI (p=0.005), but not in severe TBI (p=0.70). There was no difference in the risk of adverse events including seizures and thrombotic complications.

Strengths of this trial included its large and international sample, prespecified sensitivity analysis, and relatively complete follow-up. Limitations included its wide confidence intervals despite large sample size, potential underestimated of thrombotic complications with a lack of screening diagnostic studies, and protocol changes affecting enrolment.

Although the benefit of TXA was not shown in the overall study population, there are important lessons to be taken from this trial. First, TXA reduces bleeding-related death in patients with mild to moderate TBI. Meanwhile, those with severe TBI have a poorer overall prognosis such that TXA is unlikely to improve outcomes. Second, it is important to act fast as the benefits of TXA in mild to moderate TBI are most pronounced if given within three hours, mirroring what was seen in postpartum hemorrhage and trauma-related extracranial bleeding. Finally, TXA used at low-moderate doses does not appreciably increase the risk of thrombosis or seizures. This is consistent with a substantial body of randomized evidence reflecting the safety of TXA and suggests it should be used as frontline therapy in addition to other hematostatic measures.

I look forward to future studies examining the use of laboratory measures of fibrinolysis to appropriately target antifibrinolytic therapies. Currently available viscoelastic techniques (such as TEG and ROTEM) appear to lack sufficient sensitivity for non-severe fibrinolytic reflecting the safety of TXA and suggests it should be used as frontline therapy in addition to other hematostatic measures.
Bispecific Antibodies in Multiple Myeloma: Do These T cell–Recruiting Antibodies Make a Difference?

STUDY TITLE: Study of ISB 1342, a CD38/CD3 Bispecific Antibody, in Subjects With Previously Treated Multiple Myeloma

ISRCTN NUMBER: NCT03309111

SPONSOR: Ichnos Sciences SA

ACCRUAL GOAL: 125 patients

PARTICIPATING CENTERS: Nine centers around the United States

STUDY DESIGN: This is a phase I open-label, two part dose-escalation and cohort expansion study of ISB 1342, a bispecific antibody directed at CD38 and CD3, for patients with progressive or relapsed multiple myeloma (MM) refractory to proteasome inhibitors, immunomodulators, and daratumumab. The primary outcome measures are maximum tolerated dose defined by the number of dose-limiting toxicities, objective response according to the International Myeloma Working Group (IMWG) response criteria, and the frequency and severity of adverse events. Secondary outcomes will measure maximum serum concentration, immunogenicity by antidrug antibody formation, and disease control rate. ISB 1342 will be administered by intravenous infusion on day 1 and day 15 of each 28-day treatment cycle at escalating doses.

RATIONALE: Despite advances in the treatment of MM, current therapies fail to cure most patients with MM due to intrinsic resistance, acquired resistance, and/or persistent minimal residual disease leading to subsequent relapse. Thus, new therapies with a more potent mechanism of action are needed. Bispecific antibody therapy has proven to be clinically relevant in other hematologic malignancies through an alternative mechanism of action. In acute lymphoblastic leukemia, for instance, blinatumomab has moved into common usage before stem cell transplantation for patients with either refractory disease or with evidence of measurable residual disease. Bispecific antibodies induce redirected T-cell lysis of tumor cells by simultaneous engagement of endogenous T cells, via binding to CD3, and the tumor cell, via any extracellular tumor-associated antigen. CD3 is a tumor-associated antigen with near-universal expression in MM and has been validated as a target in MM with the human monoclonal antibody daratumumab. While daratumumab monotherapy is associated with an approximately 35 percent overall response rate (ORR) in RR when combined with other treatment modalities, not all patients respond, and many eventually develop progressive disease. The efficacy of daratumumab is limited by the inability to stimulate T-cell killing of myeloma cells. In preclinical studies, ISB 1342 was able to overcome this limitation by redirecting the cytotoxic potential of T cells to human myeloma cell lines in vitro and in mouse xenograft models. The aim of this study is to evaluate the safety, tolerability, and efficacy of monotherapy with ISB 1342 in relapsed/refractory patients.

COMMENT: The development of numerous treatment strategies aimed at overcoming the progressive immune dysfunction in myelomaogenesis has been promising. Bispecific antibodies in particular represent a powerful tool for inducing redirected T-cell–mediated antitumor activity through T-cell response against cancer. The first bispecific antibody construct with available clinical data in MM is the B-cell maturation antigen–targeting molecule AMG 420 showing a favorable adverse event profile and a 70 percent RR (7 of 10) at the recommended study dose of 400 µg. Data presented at the 2019 ASH Annual Meeting showed promising results for another B-cell maturation antigen bispecific antibody ORB-89 percent and a 44 percent complete response rate at the highest dose of 10 mg. Like AMG 420 and CC-93269, ISB 1342 is being tested in a relapsed/refractory setting. However, the efficacy of other bispecific antibody constructs have been shown to be higher in patients with less tumor burden, suggesting that earlier timing is necessary for optimal effect. Since CD3 is highly expressed in the early stages of plasma cell clonal evolution, it will be interesting to evaluate whether an anti-CD38 bispecific antibody could prevent or delay progression to symptomatic MM. However, the early expression of CD38 on other cells, such as lymphocytes, natural killer cells, dendritic cells, and bone marrow progenitor cells, raises the question of off-target toxicity. Next to timing and toxicity, resistance mechanisms due to shedding/downregulation of CD38 need to be studied further. This also raises the question of the necessity of CD38 expression upon start of treatment. Additionally, studying biomarkers for efficacy and best drug combinations will be necessary to see if an anti-CD3/CD38 bispecific antibody could be clinically successful. A second trial of a bispecific antibody dual targeting CD3 and CD3 (AMG 424) is currently recruiting (NCT03445663). Additional studies are investigating other known MM-associated antigens such as SLAMF7 and GPRC5D (NCT03397979) bispecific antibodies. While many questions remain to be answered, awaiting current trials, bispecific antibodies seem to provide an off-the-shelf alternative in the arsenal of anti-myeloma immunotherapy.

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Dr. Tahiri, Dr. Lomas, and Dr. Ghobrial noted no relevant conflicts of interest.

Dr. O’Sullivan and Dr. Mead indicated no relevant conflicts of interest.
The goal is to underscore the remarkable research that is published in Blood and to highlight the exciting progress that is being made in the field.

**JANUARY 9, 2020**

Di Buduo CA, Abbonante V, Marty C, et al. Defective interaction of mutant calreticulin and SOCE in megakaryocytes from patients with myeloproliferative neoplasms. Blood. 2020;135:133–144.

Dr. Christian A. Di Buduo and colleagues report that mutant CALR also shows loss of binding to calcium-regulatory proteins, leading to constitutive increase in intracellular calcium, further increasing proliferation of megakaryocytes, and contributing to their prominence as a clinical feature.

**JANUARY 23, 2020**

Chaturvedi S, Braunstein EM, Yuan X, et al. Complement activity and complement regulatory gene mutations are associated with thrombosis in APS and CAPS. Blood. 2020;135:239–251.

In a Plenary Paper, Dr. Shrutik Chaturvedi and colleagues provide seminal new insights into the role of complement activation in APS pathophysiology and report a high prevalence of complement-regulatory gene mutations in patients with CAPS.

**FEBRUARY 13, 2020**

Brando LR, Alibeselli M, Halton J, et al. Safety of dabigatran etexilate for the secondary prevention of venous thromboembolism in children. Blood. 2020;135:blood.201900998.

This prospective open-label study of dabigatran in children for secondary prophylaxis against venous thromboembolism (VTE) reveals low rates of recurrence and clinically significant bleeding over durations up to one year. The data suggest that dabigatran is safe for extended treatment of VTE in children and does not require routine laboratory monitoring.

**JANUARY 16, 2020**

Jaffray J, Witmer C, O’Brien SH, et al. Peripherally inserted central catheters lead to a high risk of venous thromboembolism in children. Blood. 2020;135:220–226.

This month’s CML article reports on the largest prospective observational study of long-term central venous catheter–related complications in children to date, in which this dogma is overturned. The research provides important information for decision-making about when to use central catheters and which type to choose.

**JANUARY 30, 2020**

De Stefano V, Ghirardi A, Macciulli A, et al. Arterial thrombosis in Philadelphia-negative myeloproliferative neoplasms predicts second cancer: a case-control study. Blood. 2020;135:381–386.

Patients with Philadelphia-negative myeloproliferative neoplasms are prone to the development of second cancers. In an international nested case-control study, Dr. Valerio De Stefano and colleagues identified an association between a new event of arterial thrombosis and the subsequent diagnosis of a second cancer.

**FEBRUARY 20, 2020**

Voskoboinik I, Lacaze P, Jang HS-I, et al. Prevalence and disease predisposition of p.A91V perforin in an aged population of European ancestry. Blood. 2020;135:blood.2019003487.

In a population-based analysis including a large database restricted to patients over age 70, the authors demonstrate that the A91V polymorphism in the familial hemophagocytic lymphohistiocytosis-related gene is a nonpathological polymorphism that confers no increase in cancer, death, or immunopathology.

**FEBRUARY 20, 2020**

Pan J, Zuo S, Deng B, et al. Sequential CD19-22 CAR T therapy induces sustained remission in children with r/r B-ALL. Blood. 2020;135:387–391.

Dr. Jing Pan and colleagues report one of the first prospective evaluations of planned sequential chimeric antigen receptor (CAR) T-cell therapy targeting CD19 and then CD22 in a phase 1 trial, indicating acceptable toxicity and encouraging durable efficacy in pediatric patients with relapsed/refractory (r/r) acute lymphoblastic leukemia (ALL).

**FEBRUARY 20, 2020**

Brandao LR, DelNardo CD, Stein EM, et al. Ivosidenib induces deep durable remissions in patients with newly diagnosed IDH1-mutated acute myeloid leukemia. Blood. 2020;135:blood.2019002140.

This Plenary Paper is the first publication of safety and efficacy data for ivosidenib in newly diagnosed patients until for induction chemotherapy. Dr. Gail J. Roboz and colleagues report sustained complete remissions in a substantial minority of patients. These data underpin the recent U.S. Food and Drug Administration approval for ivosidenib for this group of patients.

**Featured content from Blood Advances, Volume 4, Issue 3**

**Mutation Accumulation in Cancer Genes Relates to Nonoptimal Outcome in Chronic Myeloid Leukemia**

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm accounting for ∼15 percent of all leukemia. Progress of the disease from an indolent chronic phase to the more aggressive accelerated phase or blast phase (BP) occurs in a minority of cases and is associated with an accumulation of somatic mutations. Researchers performed genetic profiling of 85 samples and transcriptome profiling of 12 samples from 59 CML patients. They identified recurrent somatic mutations in ABL1 (37%), ASXL1 (26%), RUNX1 (16%), and BCR (16%) in the BP and observed that mutation signatures in the BP resembled those of acute myeloid leukemia (AML). The authors found that mutation load differed between the indolent and aggressive phases and that nonoptimal responders had more nonrandom mutations than did optimal responders at the time of diagnosis, as well as in follow-up. Using RNA sequencing, they identified other than BCR-ABL1 cancer-associated hybrid genes in six of the seven BP samples. Uncovered expression alterations were in turn associated with mechanisms and pathways that could be targeted in CML management and by which somatic alterations may emerge in CML. Last, they showed the value of genetic data in CML management in a personalized medicine setting.

From Awad SA, et al. Blood Advances. 2020;4: 546–559. More available at www.bloodadvances.org.
Bite Cells Abound

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A 61-year-old woman presented to clinic with fatigue, weakness, and dark urine. She underwent renal transplantation two months prior and was taking sirolimus, azathioprine, and prednisone 7.5 mg daily for immunosuppression, as well as dapsone 50 mg daily for Pneumocystis jirovecii pneumonia (PJP) prophylaxis. Glucose-6-phosphate dehydrogenase (G6PD) enzymatic activity was previously normal (15.3 U/g hemoglobin). Laboratory evaluation is shown in the Table. Ultrasound of the transplanted kidney was unremarkable. Peripheral blood smear (shown) revealed anisocytosis, frequent degmacytes (bite cells, arrows), occasional dacrocyes, and rare schistocytes (0-1/hpf).

| Test                      | Result at Baseline | Result at Presentation | Reference Range  |
|---------------------------|--------------------|------------------------|------------------|
| White blood cell count    | 10.04 × 10⁹/L      | 8.73 × 10⁹/L           | 4.00-11.00 k/µL  |
| Hemoglobin                | 12.3 g/dL          | 7.0 g/dL               | 12.0-16.0 g/dL   |
| MCV                       | 93.4               | 103.9                  | 83.0-95.0 fL     |
| Platelet count            | 357 × 10⁹/L        | 210 × 10⁹/L            | 150-450 × 10⁹/L  |
| LDH                       | 419 U/L            | 125-250 U/L            |                 |
| Haptoglobin               | <8 mg/dL           | 30-200 mg/dL           |                 |
| Reticulocytes             | 2.37%              | 5.67%                  | 0.70-2.50%       |
| Direct antiglobulin (Coombs) test | Negative       |                        |                 |
| AST                        | 26 U/L             | 45 U/L                 | 15-37 U/L       |
| ALT                        | 40 U/L             | 39 U/L                 | 13-61 U/L       |
| Creatinine                | 1.0 mg/dL          | 0.7 mg/dL              | 0.6-1.3 mg/dL   |
| Total bilirubin           | 2.7 mg/dL          | 7.0 mg/dL              | 0.2-1.0 mg/dL   |
| Direct bilirubin          | 0.4 mg/dL          | 0.0-0.5 mg/dL          |                 |
| Folic acid                | 17.8 ng/dL         | 7.0-31.1 ng/dL         |                 |
| Cytomegalovirus viral load| Negative           |                        |                 |
| Epstein Barr virus viral load | Negative      |                        |                 |
| TPMT                      | Negative           |                        |                 |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; MCV, mean cell volume; TPMT, thiopurine methyltransferase genetics.

Figure. Peripheral blood smear.

What is the most likely cause of this patient’s anemia?
A. Immune-mediated hemolysis
B. Oxidative stress-induced hemolysis
C. Bone marrow suppression
D. Nutritional deficiency
E. Thrombotic microangiopathy

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

Dr. Shantzer and Dr. Davidson indicated no relevant conflicts of interest.