Hematopoiesis is a complex, tightly regulated process of coordinated self-renewal, cell division, and differentiation from hematopoietic stem cells (HSCs) through to terminally differentiated mature blood cells, which adapts to meet needs in both homeostatic and stress contexts. While considerable focus has been placed on the hematopoietic cells themselves, hematopoiesis does not occur in isolation, but is enabled and directed by interactions with nonhematopoietic cell lineages such as the vasculature, mesenchymal stromal cells, neural elements, adipocytes, and osteolineage cells within the bone marrow microenvironment.¹

The advent of next-generation sequencing has seen the exponential expansion of knowledge of the molecular and cellular complexities of hematopoietic cells in normal and malignant contexts. Until recently, these techniques have been applied to bulk populations of cells, with inherent limitations in sequencing depth and resolution of rare cell populations, especially in admixtures of normal and malignant cells. Single-cell sequencing facilitates interrogation of cells at single-cell resolution allowing dissection of clonal composition and heterogeneity of cell populations without need for computational inferences of subclonality.²

In their recent publication, Dr. Anastasia N. Tikhonova and colleagues use single-cell and bulk mRNA sequencing to delineate spatiotemporal relationships, patterns of prohematopoietic factor production and functional consequences of gene expression changes within the bone marrow microenvironment in mice during steady-state and regenerative hematopoiesis. They couple these techniques with robust identification of cell subpopulations and functional in vitro and in vivo-correlative studies.

The authors initially isolated putative cellular HSC niche components such as blood vessels, mesenchymal stromal cells, and osteo-lineage cells to obtain single-cell sequencing data from bone marrow in steady-state conditions. T-distributed stochastic neighbor embedding analyses showed clear separation of blood vessels, mesenchymal stromal cells, and osteo-lineage subpopulations. Biomarkers were able to distinguish each of these subpopulations, even to the level of arterial vasculature versus sinusoidal capillaries or mesenchymal subpopulations. The authors even to the level of arterial vasculature versus sinusoidal capillaries or mesenchymal subpopulations. Biomarkers were able to distinguish each of these subpopulations, even to the level of arterial vasculature versus sinusoidal capillaries or mesenchymal subpopulations. The authors

1. Dr. Ling and Dr. Lane indicated no relevant conflicts of interest.

2. VICTORIA Y. LING, MBBS, FRACP, FRCPA, AND STEVEN LANE, MBBS, PHD, FRACP, FRCPA

(Cont. on page 16)
Strength in Numbers: How ASH Plans for the Future

The mission of ASH is broad: furthering the understanding, diagnosis, treatment, and prevention of blood-related disorders. Its membership is diverse: more than 17,000 hematologists from nearly 100 countries, all with heterogeneous professional needs. So how does ASH think and act creatively to keep moving forward? How do we prepare for the future while effectively managing a complex portfolio of publications, meetings, educational and training activities, advocacy efforts, and global outreach?

There is no right answer to this, and professional societies differ in their approaches. ASH relies on a large and diverse group of volunteers who represent the numerous clinical and research disciplines that touch our field. They serve on ASH committees, editorial boards, taskforces, and working groups, and provide their unique perspectives in a team-based approach to address specific aspects of our mission.

Helping to organize and harness the know-how and talents of our volunteers is the ASH staff. Ably led by our long-time executive director Martha Liggett and deputy executive director Matthew Gertzog, ASH staff members specialize in the wide variety of skills needed to keep an organization of this size moving forward, including fundraising, meeting planning, project management, accounting, and strategic development. Over the past two and a half years as an ASH officer, I have had the opportunity to attend several meetings and workshops and can bear witness to the deep and diverse talent pool serving ASH. The combination of dedicated volunteers, a robust committee structure, and a highly skilled staff is the “special sauce” that keeps ASH moving forward. Providing oversight is the ASH executive committee — five officers and eight council members elected by membership, from membership, who serve as a volunteer board of trustees for the organization.

As 2019 president, I am asked to oversee the board’s meetings and shepherd the Society as we make decisions that affect our financial outlays, our membership, and our patients. My experience has been that board members share common values and a commitment to the ASH mission. When we meet, we “put on our ASH hats” and place the best interests of the Society above self-interests or the interests of our home institutions.

Through strategic thinking, our board can rise above routine responsibilities and get to the meat of our work. We define strategic priorities, ensure that we maximize our efforts to be successful in these priorities, minimize or eliminate efforts in activities that are not strategic priorities, and identify new opportunities that align well with our mission. We listened to the voices of our members and their representatives on the board that focused the Society’s efforts on our multipronged sickle cell disease and precision medicine initiatives, the creation of Blood Advances, development of evidence-based ASH clinical practice guidelines, the ASH Foundation, and the ASH Research Collaborative. These programs are in various stages of development, from fledging to adolescence, and are positioning our Society as the long-term leading success for the professional organization for hematologists.

I learned recently that an activity that distinguishes boards that are truly exceptional is the willingness and ability to spend precious board time in “generative” discussions, designed to generate questions rather than deliver answers, and thus to identify problems before they become obvious and define future areas for strategic planning. At our annual retreat, board members, editors, standing committee chairs, and staff leaders devoted time for such discussion apart from our usual agenda, thus committing to be exceptional in our approach. Using the format of a forensic debate we discussed existential threats and opportunities that may lie ahead and how we might be better prepared to address them. We focused specifically on workforce development, asking whether hematology can continue to thrive as a “stand-alone” discipline recognized as a key specialty that brings value to clinical and research teams. We also discussed whether our strategy of positioning ASH as an umbrella society that broadly covers all areas of the discipline will remain attractive to members, as more narrowly focused societies emerge and grow. The discussion was spirited and productive and will undoubtedly lead to new ideas to test and implement.

I hope that this column serves as a reminder to the entire membership that the Society is always seeking out “new blood,” and nominations for leadership and committee positions are strongly encouraged. I hope that it also illuminates the everyday hard work that transforms the needs of members into actionable policies and programs. My experiences so far as ASH President make me confident that our Society is in good hands. We are inclusive, mission-focused, strategic, and forward thinking in our approach to governance.

T Roy L. Silverstein, MD

The Sickle Cell Clinical Trials Network: One Year In

But ASH has a great understanding of the challenges facing patients and trial development in SCD. “For me, being able to set up this network so that it will help with accrual is a key piece,” she continued, “but so is having this system where there is clear communication to industry about what the expectations should be to do these trials successfully.”

“ASH fits that great niche between industry and the community of providers who care for individuals with SCD.”

In June 2018, ASH hired Dr. Charles Chesson to serve as director of the CTN and recruited Dr. LaTasha Lee to serve as Senior Manager of Partnership Engagement. “Their first year of work has been to operationalize the endeavor, setting up the infrastructure and organizing both the patient engagement groups and nascent industry partnerships. Getting patients involved has been one of the important development milestones of the effort. So far, four of a planned eight patient engagement meetings have been undertaken. In these meetings, individuals diagnosed with SCD, and their caregivers and families discuss barriers to participation in trials and outline what they consider to be key research priorities. Following these meetings, Drs. Chesson and Lee aim to publish a comprehensive review of their findings, which will take the form of the first ever SCD Patient-Centered Research Agenda. The hope is that this agenda will influence research and be a driving factor in the development of additional treatment options for individuals living with SCD.

Simultaneous with patient engagement, the plan to approve the first wave of sites is on track and will be announced in the early fall or winter of 2019. Each of the sites is required to form a community advisory board as part of their application, ensuring that the views of parents, caregivers, teens, adolescents, and older adults with this disease are represented.

Dr. Abrams thinks that there is a growing momentum. “We’ve partnered with SCD community groups and patient national groups. We’ve met with the National Institute of Heath, the DOA on several occasions. We have met with patient groups, and more recently, we’ve been engaging local sites that potentially would be members of the network.

“There has been a lot of interest both by sites and by biotech and pharmaceutical companies,” he continued. “These milestones are getting buy-in from everyone. It’s been a joy to see that people are all stepping forward and saying, ‘We want to help with this.’”

Dr. Chesson believes that the SCDCTN is uniquely positioned. “Endorsing the CTN is a key component of the strategic plan, and we have made a commitment to provide strong organizational and financial support.”

In the first year of the network, the team has accomplished the following:

- Engaged with 36 clinical sites
- Engaged with 141 patients and caregivers
- Met with multiple stakeholders including patient representatives
- Published a review of the findings from the first patient engagement meeting
- Achieved milestones in the development of the Patient-Centered Research Agenda

The Sickle Cell CTN is a testament to the commitment of ASH to advancing research in sickle cell disease and improving outcomes for individuals living with this complex condition. The network’s success demonstrates the importance of collaboration between patients, caregivers, researchers, and the medical community to drive meaningful progress in the field.

In conclusion, the SCDCTN has made significant strides in its first year, establishing a robust infrastructure and engaging with patients and caregivers. The network’s achievements reflect the dedication of ASH to advancing research and improving care for individuals with sickle cell disease. As the network continues to grow and evolve, it will be essential to maintain the momentum and commitment to ensure that the findings of this initiative have a lasting impact on the lives of those affected by sickle cell disease.
**ASH Members Elected to the National Academy of Sciences**

The National Academy of Sciences has announced the election of 100 new members and 25 foreign associates, including two ASH members. Election to the National Academy of Sciences is considered one of the highest honors in the sciences and recognizes distinguished and continuing achievements in original research.

The two ASH members elected to the National Academy of Sciences are:

- **Timothy J. Ley, MD**
  Lewis T. and Rosalind B. Apple Chair in Oncology, Division of Oncology
  Washington University School of Medicine, St. Louis

- **Nancy A. Speck, PhD**
  Investigator, Abramson Family Cancer Research Institute; Professor, Department of Cell and Developmental Biology
  University of Pennsylvania School of Medicine, Philadelphia

**Update on the Cure Sickle Cell Initiative**

The National Heart, Lung, and Blood Institute (NHLBI) has issued a new Research Opportunity Announcement (ROA) by the institute’s Cure Sickle Cell Initiative. The overarching purpose of this ROA (OTA-19-007, “Analytical and/or Clinical Validation of Candidate Biomarkers for Curative Therapies in Sickle Cell Disease”) is to promote the validation of strong candidate biomarkers and endpoints for sickle cell disease that can be used to facilitate the development of curative genetic therapeutics from phase I through phase II/III clinical trials and in postapproval studies. The due date for applications is July 31, 2019, and applicants are encouraged to initiate the application process early.

For more information on OTA-19-007, please visit: www.curesickle.org/researchers.

**Housing Fraud Alert**

As the launch of the registration and housing website for this year’s annual meeting approaches, please keep in mind that SPARGO, Inc., is the only official housing provider for the 61st ASH Annual Meeting and Exposition. Do not be misled by “pirate” housing companies and travel agencies that aggressively pursue attendees with supposedly significant discounts. ASH has no affiliation with these organizations and does not endorse their services. Deceptive tactics by these companies include:

- Informing attendees and exhibitors that the ASH hotel room block is sold out and that if you do not book with them immediately, you may not get a room
- Distributing forms or promotional materials that appear to be issued by ASH
- Using ASH’s name and/or logo to falsely represent themselves as being affiliated with ASH
- Offering to make registration/housing arrangements for you via email

Please note that all registration and housing arrangements must be made via our secure website. Be sure the domain of the site you are on ends in **.org** or **.com**. If you encounter any of the scenarios listed, contact the ASH Housing Center immediately at ashhousing@spargoinc.com. Visit www.hematology.org/Annual-Meeting/2456.aspx for more information.

**2019 ASH Annual Meeting Upcoming Deadlines**

The 61st ASH Annual Meeting will take place December 7-10, 2019, in Orlando. The meeting will provide an invaluable educational experience and the opportunity to review thousands of scientific abstracts highlighting updates in the hottest topics in hematology. Attendees can also network with top minds in the field as well as a global community of more than 25,000 hematology professionals from every subspecialty. Visit www.hematology.org/Annual-Meeting for more information and to see what’s in store this year in Orlando.

- **ASH Foundation Run/Walk registration opens** – July 10, 2019, 11:00 a.m. Eastern Time
- **Members-only registration and housing opens** – July 24, 2019, 11:00 a.m. Eastern Time
- **Abstract submission deadline** – August 1, 2019, 11:59 p.m. Pacific Time
- **Advance registration and housing open for nonmembers** – August 14, 2019, 11:00 a.m. Eastern Time
- **Call for late-breaking abstract submissions** – October 21-31, 2019


Various recommendations for pain management in patients with sickle cell disease (SCD) proposed by ASH were included in the final report. The report also highlighted a clarification from the Centers for Disease Control and Prevention (CDC) stating that the CDC Guideline for Prescribing Opioids for Chronic Pain is not meant to deny clinically appropriate opioid therapy to any patient who suffers acute or chronic pain from conditions such as cancer or SCD, but was developed with the purpose of providing recommendations for primary care clinicians who prescribe opioids for patients with chronic pain outside of active cancer treatment, palliative care, and end-of-life care.

To access the final report, visit www.hhs.gov/ash/advisory-committees/pain-reports/index.html. You can also find an informative Q&A with Dr. Vanila Singh, the Chief Medical Officer of the HHS Office of the Assistant Secretary of Health and Chairperson of the Pain Management Inter-Agency Task Force, at www.hhs.gov/blog/2019/05/10/patient-centered-care-is-key-to-best-practices-in-pain-management.html.
The Case
A 46-year-old woman with a long history of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma since 2011 presented urgently to a local hospital after being found unresponsive in her bedroom by family. Cardiopulmonary resuscitation was started immediately, emergency medical services were quickly notified, and she was defibrillated, intubated, and stabilized throughout the next 48 hours. The presenting rhythm identified by EMS was ventricular fibrillation. A cardiac catheterization was done that revealed normal coronary arteries, and the only major finding was that her left ventricular end diastolic pressure was 25 mm Hg (normal, < 12 mm Hg). An electrocardiogram (ECG) done the next day indicated overall normal left ventricular function (left ventricular ejection fraction, 55%). A subcutaneous implantable cardioverter defibrillator (ICD) was implanted the next day without difficulty. One week later, she was healing well from any wounds, and the ICD was functioning appropriately.

Her medical history was notable for CLL/small lymphocytic lymphoma, with her initial presentation in November 2011 with peripheral lymphocytosis and lymphadenopathy; the florescence in situ hybridization was negative. Her treatment included fludarabine and six cycles of rituxan from December 2011 to May 2012, with a complete response. She then had recurrent disease with diffuse lymphadenopathy and bone marrow involvement noted in May 2015. Ibrutinib 420 mg was administered from May 2015 to present, and computed tomography was done that revealed normal coronary arteries, and the next 48 hours. The presenting rhythm identified by EMS was ventricular fibrillation. A cardiac catheterization was done that revealed normal coronary arteries, and the only major finding was that her left ventricular end diastolic pressure was 25 mm Hg (normal, < 12 mm Hg). An electrocardiogram (ECG) done the next day indicated overall normal left ventricular function (left ventricular ejection fraction, 55%). A subcutaneous implantable cardioverter defibrillator (ICD) was implanted the next day without difficulty. One week later, she was healing well from any wounds, and the ICD was functioning appropriately.

Of note, her other medications included dextroamphetamine-amphetamine, synthroid, and desvenlafaxine ER. Additionally, she reported drinking alcohol heavily for three days prior to her cardiac arrest.

The Question
Does ibrutinib therapy increase the risk of serious rhythm disturbances?

The Response
The question of whether ibrutinib is causative of atrial fibrillation has been the subject of much discussion and investigation. Several articles have suggested that it might occur quite frequently in patients with CLL, in one study up to 13 percent, and the consequences of atrial fibrillation in patients who were on ibrutinib resulted in a high percentage having to discontinue therapy, most commonly owing to an increase in bleeding events. It is very clear that ibrutinib therapy is associated with a higher rate of atrial fibrillation than the "ambient" rate found in patients with CLL who are not on that therapy, and the risk of bleeding is a particularly vexing problem that may lead to discontinuation of this treatment. What is particularly challenging in this case is whether ibrutinib is associated with a more serious and life threatening rhythm disturbance than just atrial fibrillation. As it turned out, in this patient, there was an episode of sudden death in which she was quickly and effectively resuscitated. This is very good news, however, from a detailed history and extensive evaluation, the cause of ventricular tachycardia or ventricular fibrillation (VT/VF) was not apparent. She had no structural reason for VT (normal left ventricular ejection fraction and normal valvular structures) but was on ibrutinib and dextroamphetamine-amphetamine (a powerful stimulant). She did have significant alcohol exposure, and that certainly may have contributed. Her baseline ECG in 2014 and the repeat after the event in May 2019 did not reveal any major abnormalities other than nonspecific anterior T wave changes (Figure 1). When a topical wireless monitor was placed, the QT interval appeared prolonged and varied significantly when accessed via the transmission (Figure 2, black arrows). It has been observed that ibrutinib may be associated with VT, but it is not clear that it is a prolonged QT-based mechanism. Furthermore, this patient had not been on ibrutinib for more than two weeks on the May 2019 ECG or when the wireless monitor was placed.

Recommendations
It is difficult to associate VT or sudden death with a particular medication. As is frequently the story in cases of sudden cardiac death, there are many possible explanations. In this case, the patient was on ibrutinib, but also dextroamphetamine-amphetamine and had significant alcohol exposure. Exactly what was required to create the milieu for a “perfect storm” and resultant VT is conjecture. After the event, it appeared as though she did have intermittent prolongation of the QT interval that is only detected with prolonged monitoring. Her future therapy for CLL should probably be an alternative agent, mainly because this sudden death event is at least possibly associated with ibrutinib. Nevertheless, it is difficult to identify a safe drug if there are no telltale signs on the baseline standard 12-lead ECG. This case highlights that a topical patch monitoring system for an extended period may identify important findings to establish a connection between a medication and serious rhythm disturbances.

It is unlikely that such an association could ever be established with an intermittent 12-lead ECG as is the current standard recommendation.

Autoimmune Disorders and the Development of Myeloid Disease: Should We Always Blame the Therapy?

The Case

A 64-year-old woman was referred to our clinic with pancytopenia and fatigue. The patient reported a four-year history of systemic lupus erythematosus (SLE; synovitis, malar rash, oral ulcers, pleural effusions, anti-Smith antibody) that had previously been treated with pulse cyclophosphamide and concomitant oral prednisolone followed by maintenance azathioprine for severe nephritis. The bone marrow (BM) aspiration at diagnosis showed 56 percent blasts consistent with acute myeloid leukemia (AML). BM cytogenetics showed a monosomy 7 deletion. Azathioprine was promptly discontinued. Molecular testing revealed lack of NPM1, FLT3, CEBPA, or TP53 mutations and presence of pathologic mutations in DNMT3A and ASXL1. After detailed discussion with the patient about lower- and higher-intensity therapy options in the context of adverse cytogenetics with monosomy 7, she elected to proceed with intensive chemotherapy, to be followed by allogeneic hematopoietic stem cell transplantation.

This case illustrates one of the dreaded downstream events in individuals with severe autoimmune disease (AD) — the development of therapy-related myeloid neoplasm (t-MN). An elevated risk of AML/myelodysplastic syndromes (MDS) has been reported across several ADs, including SLE, rheumatoid arthritis (RA), inflammatory bowel disease, and multiple sclerosis. Large scale population-based studies have shown the risk to be between 1.3 and 2.1 in patients with a previous history of AD compared to population baseline. Historically, this risk has been tied to given cytotoxic therapies, but that is likely too simple. Rather, current thought is that genetic susceptibilities, immune stimulation of the BM, and immune surveillance defects cooperate in the development of t-MN. Supporting this is the era of emergence of myeloid malignancies in the natural course of AD and development of MDS/AML among patients who have had no prior treatment exposure for their AD.

Etiologies

One of the first questions that this patient and others will ask is why t-MN occurs? For years, many hematologists blamed prior treatment; however, it is increasingly understood that there is a multifactorial pathogenesis to AD-associated MN development. The risk of t-MN varies by the type of AD and the duration and type of genotoxic agent exposure. Among the commonly used drug classes in the management of AD, secondary leukemogenesis has been described extensively with the use of alkylating agents (cyclophosphamide), antimetabolites (azathioprine), and topoisomerase inhibitors (mitoxantrone). For example, prior azathioprine exposure has been associated with as high as a sevenfold elevated risk compared to the population baseline, possibly due to direct DNA mutagenic effects. However, it is not just the treatment. Leukemogenic susceptibility to genotoxic agent exposure is strongly influenced by individual genetic predisposing factors. These factors include metabolism phenotypes, DNA damage repair pathways, and possibly the concomitant presence of clonal hematopoiesis of indeterminate potential (CHIP). Patients with preleukemic CHIP have a significantly higher risk of developing t-MNs than patients without clonal hematopoiesis, and screening for CHIP at the time of primary cancer diagnosis can help identify patients at risk for t-MN. The risk of t-MN in breast cancer and Hodgkin lymphoma survivors is correlated with the extent of radiotherapy and the duration and type of chemotherapy. Importantly, the elevated risk of MN with conventional cytotoxic therapies does not seem to be shared by biologic therapies such as tumor necrosis factor-alpha (TNF-α) inhibitors.

What about treatment-naïve patients? One hypothesis is that HLA-associated susceptibility can partially explain the occurrence of AML in patients with AD who have never been treated or who avoid cytotoxic agents. For example, HLA-B27 carrier status has been associated with an increased predisposition to both AD and AML. Another important molecule implicated in hematologic malignancies (HMs) involving the myeloid lineage is interleukin-1 receptor antagonist gene that has been associated with both AD and secondary AML. The BM microenvironment is known to play an important role in AML/MDS pathogenesis and progression. A profound inflammatory tumor microenvironment can contribute to overall tumor progression by promoting various aspects of cancer cell proliferation and survival. A central proinflammatory mediator, implicated in both ADs^1^ and leukemias, is nuclear factor-κα (NF-κα). Constitutive NF-κα signaling can be achieved either through intracellular autogenic activation or extrinsically by cytokine factors produced in the tumor microenvironment milieu. Finally, leukemic myeloid cells develop a variety of escape mechanisms to evade peripheral T-cell immune surveillance and destruction. Further impairment of a disrupted T-cell immunologic surveillance by exposing the BM to immunosuppressive agents could potentially lead to their clinical emergence.

SLE and t-MN

Only a few studies have specifically investigated the risk of myeloid leukemia in SLE, which is the pre-existing condition in this case. Analyses by Dr. Lena Björnård and colleagues and Dr. Arnt Parikh-Patel and colleagues reported an elevated risk of myeloid leukemia in SLE, with a standard incidence ratio of 3.4 and 2.96, respectively. Similarly, Dr. Björn Löfdström and colleagues reported an increased risk of AML in a Swedish national cohort of 6,438 patients with SLE. Notably, the leukemia risk in this study was confined to the patient subset with preceding prolonged cytopenias, especially leukemia. The median latency period between SLE and leukemia diagnoses was five years. The risk of myeloid leukemia was restricted to the subgroup characterized by more men and older age at onset of SLE. Further, the study did not identify a difference in the frequency of cytotoxic exposure between the case and control cohorts, suggesting that prior cytotoxic exposure is not a major cause for AML development in SLE. Another study investigated the effect of latency of AML development in SLE and showed a decremental risk for myeloid leukemias with longer SLE latency.

Newer Treatments for AD?

Another question that arises, especially during consultation on cases of AD, is whether or not there are increased risks when the agents dubbed “disease-modifying antirheumatic drugs” (DMARDs) are used. These medications are commonly used in patients with RA and in conditions such as ankylosing spondylitis, psoriatic arthritis, and SLE. While data on the increased risk of development of certain cancer types (e.g., melanoma, nonmelanomatous skin cancers, and lymphomas in patients with RA treated with anti-TNF-α therapy) are conflicting, there is no substantial increase in the risk of leukemias in patients treated with anti-TNF-α therapy as compared with those treated with any nonbiological DMARDs. In a Swedish Cancer Registry study by Dr. Johan Askling and colleagues, a significant association between RA and AML risk was observed only in the inpatient advanced and early-arthritis cohorts, but not in the TNF-α-blocker group, which argues for a DMARD approach as a critical risk factor in AML development. Data from the same study also suggested no effect of RA latency on the risk for AMLs. While a significant, albeit weak, association between DMARD use and HM risk has been noted with azathioprine and cyclophosphamide therapies, the occurrence of leukemia cases even among patients who had had no prior exposure to cyclophosphamide or azathioprine suggests a link to RA-related immune stimulation itself.

Future Directions

The excess risk of MNS in AD varies by the particular type of AD, reflecting biologic differences between AD entities. Unfortunately, studies designed to investigate the role of...
AD-directed therapy in MN risk have yielded conflicting results, and data correlating patient and AD features with subsequent MN development are not forthcoming. Additionally, we still do not have a complete understanding of the molecular defects underpinning secondary leukemogenesis in AD. Important future research agendas include evaluation of molecular defects and identification of risk factors associated with MN development in AD. A more detailed characterization of biologic mechanisms through focused efforts directed toward delineating pathophysiologic pathways will not only further our understanding of the association between the two entities but also help identify patients who are at a higher risk for developing post-AD MNs and who may therefore benefit from preemptive strategies, especially now with the availability of potentially safer and more effective biologic treatment alternatives.

Editors’ Note: This feature is based on a more robust review article published in March 2019 in Best Practice & Research Clinical Haematology. The authors are B. Stuhler, I. T. Pedersen-Bjergaard, A. M. S. Andersen, and C. M. J. Nyhus. The article discusses the role of autoimmunity in myeloid leukemia and highlights the importance of understanding the pathogenesis of this interaction.

Sickle Cell Disease Clinician Speaks on Why Advocacy Is Critical to Her Patients

In recent years, issues affecting patients with sickle cell disease (SCD) have become a key focus of ASH’s advocacy work in Washington, DC. The Society continuously works with federal agencies and the U.S. Congress to encourage expansion of government activities in SCD research, training, and services. Late last year, in the final days of the 115th Congress, ASH achieved a major advocacy victory with the Sickle Cell Disease and Other Heritable Blood Disorders Research, Surveillance, Prevention, and Treatment Act of 2018 (P.L. 115-327) being signed into law. The law authorizes SCD prevention and treatment grants awarded by the Health Resources and Services Administration (HRSA) and authorizes the federal government to award data collection grants via the Centers for Disease Control and Prevention (CDC). This achievement could not have been possible without the help of Society members who called and wrote letters to their elected officials. The Hematologist spoke with one of the Society’s most vocal SCD advocates, Dr. Julie Kanter, to discuss her success speaking out on behalf of patients with SCD.

Dr. Kanter, a hematologist at the University of Alabama in Birmingham and a member of the ASH Committee on Government Affairs and the ASH Grassroots Network, recently played a key role in the Society’s efforts to pass federal legislation to advance care for patients with SCD.

Dr. Kanter first became involved in advocacy to speak out on behalf of her patients. “My research and clinical focus is in SCD. I don’t think you can focus on [SCD] and not realize the importance of advocacy,” she said. “As a rare disease with multiple health disparities it is just as important that we advocate for patients’ rights as it is that we care for these individuals.”

Dr. Kanter expanded her role in advocacy in 2015 after participating in the ASH Advocacy Leadership Institute (ALI), a two-day program in Washington, DC, that allows ASH members to learn how to be effective hematology advocates. “ALI taught me a lot about how to advocate for patients effectively, and I continue to work with government figures and participate in congressional briefings,” she said. “I think ASH has made me a much better advocate.”

Before moving to Alabama earlier this year, Dr. Kanter lived in South Carolina where she fostered a strong working relationship with one of the sponsors of the Sickle Cell Disease and Other Heritable Blood Disorders Research, Surveillance, Prevention, and Treatment Act of 2018, Senator Tim Scott. “I knew that working closely with the congressional delegation in my state before coming to South Carolina,” explained Dr. Kanter. However, “collaboration with ASH and my university’s government relations sponsor were instrumental in ensuring I was introduced to the right people and kept important legislation in front of them.”

Dr. Kanter reached out to the senator’s office regularly, offering to serve as an expert for the senator and his staff on issues related to health care and SCD. “I frequently communicated with Senator Scott and his staff and continued to keep in touch with [members of the senator’s] staff even if they moved on to other offices,” she said. “It took multiple meetings and ongoing presence, but it was effective in conveying what was important.” Her efforts eventually led to Senator Scott agreeing to introduce the abovementioned SCD legislation, along with Senator Cory Booker (D-NJ). “It is one of the few times I really felt that our government worked the way it should,” Dr. Kanter said.

Since moving to Alabama, Dr. Kanter has wasted no time in introducing herself to the state’s two senators and her new representative. “I wanted to meet the congressional delegation as soon as possible after moving to Alabama,” she recalled. “I think it is important that they understand the work I am trying to do for our patients and the population in general.”

Dr. Kanter plans to meet with her new state legislative delegation at well. While usually less well-known than their federal counterparts, state-level legislators still hold considerable sway over laws that affect patients and hematology research and practice.

Are you interested in becoming more involved in advocacy, either in Washington or in your home state? Start by joining the ASH Grassroots Network to receive regular updates and information about how to contact your members of Congress. Visit the ASH Advocacy Center at www.hematology.org/advocacy to learn more.
Three Identical Strangers, One Pressing Question

KRISTEN O’Dwyer, MD
Assistant Professor of Medicine, Wilmot Cancer Institute, University of Rochester, Rochester, NY

Interest in documentaries has been on the upswing, as anyone who follows podcasts or subscription television can attest. It’s not just technology, the increasing number of media platforms, or the incredibly expanding amount of contemporary footage that has fueled this turnaround. The format of the documentary provides something that neither fiction nor newscasts can accomplish. While broadcast news may be able to deliver the current truth or a vision of it, documentaries provide scope. They look backward across long periods, which allows viewers to see the entire historical picture compressed and illuminated. Unlike fiction, where the bargain with the reader is that something recognizable but unreal will happen, documentaries ask us to acknowledge what is true.

Reclaimed footage, a compelling story, and innovative direction can spotlight stories that might have been otherwise forgotten. At their best, they can also force us viewers to rethink the present. That’s what happened to me on viewing “Three Identical Strangers,” a 2018 documentary film that has remained among the most popular offerings on Netflix since its release. (Spoiler alert: Those who would like to watch the film without spoilers should do so now before reading further.)

The story tells of triplet boys born to a teenage single mother in 1961, relinquished to an adoption agency in New York City, and placed in separate adoptive families. Neither the families nor the boys — Eddy Galland, David Shafran, and Robert “Bobby” Shafran — were told of the other identical siblings’ existence, but a chance encounter by my visceral response as a parent. Footage of the triplets sharing a crib in their infancy juxtaposed with interviews by my visceral response as a parent. Footage of the triplets sharing a crib in their infancy juxtaposed with interviews

Having been invited to write this essay and discuss how the movie affected my professional worldview, I can report my distressed reaction as a clinical researcher was eclipsed by my visceral response as a parent. Footage of the triplets sharing a crib in their infancy juxtaposed with interviews...
X-linked severe combined immunodeficiency (X-SCID) is a rare inherited disorder of the immune system caused by mutations in the common γ chain (IL2RG). This condition is characterized by near-absent T and natural killer (NK) cells with present but dysfunctional B cells. Without immune reconstitution, X-SCID is generally fatal in the first year of life. The standard of care for X-SCID is allogeneic hematopoietic cell transplantation (HCT), with best outcomes achieved using HLA-matched sibling donors (MSD). However, loss of 20 percent of infants will have an MSD, and transplantation with unrelated and haploidentical donors is complicated by increased rates of graft-versus-host disease (GVHD) and delayed immune reconstitution. Furthermore, high-dose chemotherapy is required for B-cell reconstitution in these patients, raising concerns for potential late effects related to the use of alkylating agents in early infancy.

Gene therapy is an appealing alternative for infants without an MSD because it allows for use of milder conditioning regimens and eliminates the risk of GVHD, abrogating the need for immunosuppressive therapy. Early gene therapy trials in Europe using viral g-retroviral vectors without conditioning demonstrated successful reconstitution of the T-cell compartment in patients with X-SCID. However, five of 20 patients developed T-cell leukemia due to insertional oncogenesis; one patient died, and all patients remained dependent on immunoglobulin replacement. A subsequent international trial using a self-inactivating (SIN) γ-retroviral vector had an improved safety profile with no reports of myelodysplasia or leukemic transformation; however, immunodeficiency was not restored in the absence of chemotherapy conditioning. More recently, Dr. Suk See De Ravin and colleagues at the National Institutes of Health (NIH) used a SIN-lentiviral vector with low-dose busulfan conditioning to treat five older male patients ranging from seven to 23 years of age with persistent immunodeficiency despite haploidentical HCT in infancy. Encouragingly, follow-up from the two older patients demonstrated complete T- and B-cell reconstitution with clinical improvement and independence from immunoglobulin replacement.

Dr. Evelina Mamcarz and colleagues presented results of a dual-center, phase II clinical trial out of St. Jude Children’s Research Hospital and the University of California, San Francisco observing SIN-lentiviral gene therapy in eight consecutive male infants newly diagnosed with X-SCID and without an MSD. The group used the same lentiviral vector as the NIH to transduce bone marrow–derived CD34+ cells and low-dose targeted busulfan with a goal area under the curve (AUC) of 22 mg × h/L. Median age at gene therapy was 3.5 months (range, 2-14 months). Interestingly, three patients had maternal T-cell engraftment, and five had a history of previous infection, including one patient with active cytomegalovirus (CMV) and two patients with active disseminated bacille Calmette-Guérin (BCG) at time of gene therapy. Median CD34+ cell dose was 6.73 × 10^6/kg (range, 4.46-15.10 × 10^6/kg) and median vector copy number (VCN) was 0.40 per CD34+ cell (range, 0.16-1.13 per CD34+ cell). Conditioning was well tolerated with no significant busulfan-related toxicity, and all patients were engrafted without the need for blood product transfusions. There were no significant new immune complications, and the preexisting CMV and BCG infections were resolved with immune recovery. All patients were alive at a median follow-up of 16.4 months (range, 6.7-24.9 months). VCN has remained stable with time, and vector integration site analyses demonstrated highly polyclonal integration patterns in all patients.

One patient had persistent maternal T cell engraftment and received a gene therapy boost 12 months after his first infusion with improvement in vector-marked T cells. Of note, this patient received the lowest CD34+ cell dose and had the lowest VCN of the graft. T-cell recovery was rapid in the remaining seven patients with all patients achieving normal T-cell subset counts (CD8+, CD4+, CD8+ in two to four months after infusion, including normal naive T-cell counts (CD3+, CD4+, CD8+)) within 10-19 months after gene therapy. T-cell proliferation to phytohemagglutinin was normal by four months. Spectratyping demonstrated polyclonal TCR-Vβ repertoires in all patients. B-cell recovery was also rapid with normal B-cell counts by two months, and four patients were able to come off intravenous immunoglobulin replacement (IVIG) at 15 to 23 months after gene therapy. Three patients have also mounted protective antibody responses to vaccines, indicative of functional T- and B-cell reconstitution.

In summary, early results from this phase II trial are encouraging, with 100 percent survival and seven of eight patients achieving rapid and robust T- and B-cell reconstitution following SIN-lentiviral gene therapy with low-dose busulfan. Immune reconstitution was more rapid than that typically seen following T-cell depleted unrelated and haploidentical donor HCT, and there were no cases of viral reactivation in this trial. Reassuringly, vector integration site analyses have demonstrated polyclonal integration patterns with no clonal expansions, though follow-up is Encouragingly, follow-up from the two older patients demonstrated complete T- and B-cell reconstitution with clinical improvement and independence from immunoglobulin replacement.

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

DANIELLE E. ARNOLD, MD, AND DAVID T. TEACHEY, MD

X-linked severe combined immunodeficiency (X-SCID) is a rare inherited disorder of the immune system caused by mutations in the common γ chain (IL2RG). This condition is characterized by near-absent T and natural killer (NK) cells present but dysfunctional B cells. Without immune reconstitution, X-SCID is generally fatal in the first year of life. The standard of care for X-SCID is allogeneic hematopoietic cell transplantation (HCT), with best outcomes achieved using HLA-matched sibling donors (MSD). However, loss of 20 percent of infants will have an MSD, and transplantation with unrelated and haploidentical donors is complicated by increased rates of graft-versus-host disease (GVHD) and delayed immune reconstitution. Furthermore, high-dose chemotherapy is required for B-cell reconstitution in these patients, raising concerns for potential late effects related to the use of alkylating agents in early infancy.

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In summary, early results from this phase II trial are encouraging, with 100 percent survival and seven of eight patients achieving rapid and robust T- and B-cell reconstitution following SIN-lentiviral gene therapy with low-dose busulfan. Immune reconstitution was more rapid than that typically seen following T-cell depleted unrelated and haploidentical donor HCT, and there were no cases of viral reactivation in this trial. Reassuringly, vector integration site analyses have demonstrated polyclonal integration patterns with no clonal expansions, though follow-up is admittedly short. Ultimately, long-term follow-up is needed to demonstrate durability of immune reconstitution and long-term safety of the lentiviral vector product. Nevertheless, results from this trial suggest that gene therapy is a viable treatment option for X-SCID patients without an MSD and may be superior to HCT with alternative donors. As more patients are treated with gene therapy and as safety and efficacy improve, one can foresee a time when gene therapy becomes the new standard of care for X-SCID. As safety and efficacy improve, one can foresee a time when gene therapy becomes the new standard of care for X-SCID.

Dr. Arnold and Dr. Teachey indicated no relevant conflicts of interest.
Is Double-hit Diffuse Large B-cell Lymphoma More Common Than We Think?

Dr. Daisuke Ennishi and colleagues investigated the biologic differences between garden variety GCB DLBCL and DH DLBCL by analyzing cases through targeted resequencing, whole-exome sequencing, RNA sequencing, and immunohistochemistry. In the process, they uncovered a group of patients who did not meet the classical definition of DH DLBCL but who had gene expression signatures very similar to DH DLBCL and clinical outcomes very similar to DH DLBCL. By this broader definition, the proportion of patients with a DH signature approximately doubles.

So, what are the biologic underpinnings of this new entity? The authors noted a distinct mutational landscape that comprises several genes associated with chromatin remodeling. They also noted overexpression of MYC and EZF target genes, as well as genes associated with oxidative phosphorylation and high metabolism. They observed low expression of genes associated with immune signatures and inflammatory signatures. Despite the MYC signatures by gene expression profiles and mutational analysis, MYC rearrangements were not present by FISH testing, suggesting other mechanisms for MYC dysregulation. Embedded in this biology are some suggestions of therapeutic strategies to exploit (histone modifying agents) and avoid (immunotherapy).

So, should the definition of this low-prognosis DLBCL be revised from “DH DLBCL” to “DH signature DLBCL”? This change would create a new, larger category with about half of all DLBCL cases.

References:

Dr. Brierley and Dr. Mead indicated no relevant conflicts of interest.

Figure 1

Piecing Together the Bone Marrow Niche

were further able to trace differentiation of these latter cell populations along a continuum using relative expression of various differentiation markers. To ascertain interactions between the microenvironment and hematopoietic cells, they profiled expression levels of hematopoietic factors with individual cells and populations, identifying the specific populations that produce factors with known functions in the cell extrinsic support of HSCs, such as stem cell factor and stromal cell-derived factor 1. To determine changes during stress hematopoiesis, mice were given a marrow-ablating dose of 5-fluorouracil and the analysis was repeated. In this case, the authors observed an adipocyte-primed cluster not present at steady-state and a global reduction in the osteolineage. They saw an increase in active cycling cells pre-empting bone marrow regeneration, together with changes in expression of hematopoietic factors, identifying changes in Wnt and Notch signaling. Specifically, Notch ligand, Dll4, expressed only in the vascular cells, was downregulated by chemotherapy treatment. These findings were functionally validated by inducibly deleting Dll4 on mouse niche cells. This resulted in changes within hematopoietic progenitor cell frequencies, specifically leading to myeloid-biased changes and concomitant loss of lymphoid differentiation.

In aggregate, Dr. Tikhonova and colleagues define spatiotemporal transcriptional profiles of distinct subpopulations of the bone marrow niche at single-cell resolution, providing unprecedented detail into the dynamic, complex interactions of the bone marrow microenvironment. These mechanistic insights are elegantly translated using genetically modified mouse models, demonstrating the integral functions of Dll4 in hematopoiesis, particularly after chemotherapy.

The study helps to piece together the complex, three-dimensional, living jigsaw puzzle that is the bone marrow HSC niche, highlighting the integral roles of these cells in supporting hematopoiesis and health and disease. The level of detail of the bone marrow microenvironment provides opportunities for discovery of cellular interactions that can be targeted therapeutically in the clinical real and raises new questions. For example, are there aberrant interactions present that maintain leukemia and leukemic stem cells? How do prohematopoietic signaling from the microenvironment promote bone marrow regeneration following cytotoxic or immunogenic insults? Can age-related decline in HSC function be stalled or reversed?

Single-cell sequencing is currently limited in the number of cells that can be studied (thousands to tens of thousands), but can uniquely provide resolution to detect subtle changes within small subpopulations of cells and will build on bulk sequencing studies. The data and techniques showcased in Dr. Tikhonova and colleagues’ study represent seminal gains in knowledge into the hematopoietic microenvironment and have wide-ranging significance for future studies into normal blood formation, ageing, bone marrow regeneration, and hematopoietic malignancies.

References:
2. Morrison SJ, Scadden DT. The bone marrow niche for hematopoietic wide-ranging significance for future studies into normal hematopoietic microenvironment and have maintained long-term remission, with relapse rates of approximately 35% (range, 21-50%) reported in phase I and II clinical trials. Although the clinical characteristics and laboratory biomarkers that determine the duration of the antimarrow responses of CART therapy have not been specifically defined, successful long-term remission linked to CAR T-cell persistence beyond the induction of CR is disease burden at the time of T-cell infusion. Although, whether additional consolidation therapy in the form of allogeneic hematopoietic stem cell transplantation (allo-HSCT) is required and/or beneficial for all relapsed B-ALL patients following CART therapy has not been determined and remains an important unanswered clinical question. Thus, the understanding of the clinical and laboratory variables that contribute to long-term remission will help define the optimal use of CART immunotherapy for children and adults with B-ALL.

On the Road to a Better CAR: Identifying the Variables Associated With a Durable Response to CART T-Cell Therapy in Relapsed/Refractory B-ALL


C

D19-directed chimeric antigen receptor T-cell (CAR-T) therapy induces complete remission (CR) in approximately 80% of children and adults with relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL). In these responders, approximately 70% (range, 53-93%) have no detectable minimal residual disease (MRD) by multiparameter flow cytometry.1 Robustly induced T-cell expansion, followed by a clonal and targeted cytotoxic attack of the CD19 lymphoblasts, is the likely mechanism associated with high remission rates. However, T-cell counts will maintain long-term remission, with relapse rates of approximately 35% (range, 21-50%) reported in phase I and II clinical trials. Although the clinical characteristics and laboratory biomarkers that determine the duration of the antimarrow responses of CART therapy have not been specifically defined, successful long-term remission linked to CAR T-cell persistence beyond the induction of CR is disease burden at the time of T-cell infusion. Although, whether additional consolidation therapy in the form of allogeneic hematopoietic stem cell transplantation (allo-HSCT) is required and/or beneficial for all relapsed B-ALL patients following CART therapy has not been determined and remains an important unanswered clinical question. Thus, the understanding of the clinical and laboratory variables that contribute to long-term remission will help define the optimal use of CART immunotherapy for children and adults with B-ALL.

Dr. Hay and colleagues have provided important long-term follow-up data on their cohort of adult patients with relapsed/refractory B-ALL and examined the variables associated with a durable CART therapy response. The authors identified lower serum LDH concentration, higher platelet count prior to lymphodepleting chemotherapy, and the use of fludarabine in the lymphodepleting chemotherapy regimen to be associated with durable remissions. The relationship between a lower serum LDH and a higher platelet count as well as a higher frequency of durable remissions suggests that aggressive disease kinetics and tumor burden and the cumulative effects of prior salvage regimens on the marrow may limit CART therapeutic effects. The use of fludarabine in lymphodepleting chemotherapy has been associated with CAR T-cell expansion and persistence,2 and these follow-up data support that association. Additionally, a multivariable analysis associated allo-HCT with better EFS in patients in MRD-negative CR following CART therapy. Confirmation of the results of this study will require a larger cohort of patients. Detection and quantification of MRD is needed for consolidation treatment after CD19 CART therapy in the relapsed patient will require randomized clinical trials.

References:
Superficial Thrombophlebitis: The Less Dangerous Cousin of Deep Vein Thrombosis That Can Still Cause Harm


Superficial thrombophlebitis (ST) is a painful thrombotic condition that presents as a tender, erythematous, palpable cord with localized edema. Unlike patients with acute deep vein thrombosis (DVT), patients with ST do not necessarily require anticoagulation. How then do we decide which patients require anticoagulant therapy? And if anticoagulants are recommended, which agent, dose, and duration should be prescribed?

The decision to prescribe anticoagulants for superficial thrombophlebitis is primarily based on the risk of progression into the deep venous system. Factors such as length of the ST (~5 cm), proximity to junction with the deep veins (<3 cm from saphenofemoral junction or perforator veins within the popliteal fossa), pregnancy, hormones, active inflammatory disease, prior venous thromboembolism (VTE) or ST, and active cancer increase the potential for progression. Patients without any of these risk factors can generally be treated with pain control measures (topical nonsteroidal anti-inflammatory drugs [NSAIDs] and compresses) in addition to clinical surveillance for worsening of symptoms. For patients with one or more of these risk factors, guidelines suggest anticoagulants be considered.1,2

To answer the question of which agent to use for treatment of ST, Dr. Marcello Di Nisio and colleagues recently published a clinical synopsis of their Cochrane review.3 Randomized controlled trials evaluating low-molecular-weight heparin (LMWH), fondaparinux, rivaroxaban, hirapin spray gel, tenoxacin, naproxen, graduated compression stockings, and saphenofemoral disconnection were included in the review. The primary outcome measure was symptomatic VTE. Secondary outcome measures included ST extension, progression, and symptom control.

In brief, when compared with placebo, only fondaparinux reduced the risk of symptomatic VTE;1 whereas fondaparinux, LMWH, and NSAIADs all reduced the risk of ST extension (Table). The largest trial comparing two active treatments showed no difference between fondaparinux 2.5 mg daily and rivaroxaban 10 mg daily for symptomatic VTE or ST extension.1 There was insufficient evidence for all other treatments. Key limitations for the two largest trials included restriction of enrollment to low-risk patients in the fondaparinux versus placebo trial,3 and the small number of events in the rivaroxaban trial.1

The clinical synopsis by Dr. Di Nisio and colleagues shows that the jury is still out on the right agent to use for treatment of ST. Fondaparinux is the most promising to date, but it requires 45 days of costly injections for a 1 percent absolute risk reduction for VTE.

My personal approach to treating ST starts with a risk assessment (site and length of the ST; risk factors as mentioned previously) followed by an ultrasound to exclude DVT (unless an isolated short segment confined to a varicose vein below the knee). If the ST is larger than or equal to 5 cm long and/or within 3 cm of the saphenofemoral junction, I perform a risk assessment for bleeding. If the risk of bleeding is low, I recommend either fondaparinux or rivaroxaban for 45 days (for pregnant patients LMWH is a safe alternative). If the bleeding risk is high, I arrange for a repeat ultrasound within five to seven days to rule out progression into the deep veins.

For all patients, I recommend topical diclofenac four times daily because I find it offers better pain control than oral NSAIDs, with fewer adverse effects. Duration of treatment is continued beyond 45 days if pain continues, but it is not based on resolution of the palpable cord (which turns brown and is no longer tender) or of ultrasound abnormalities, which can persist indefinitely. Lastly, I review the symptoms of VTE. Upper extremity superficial thrombophlebitis was not covered in the referenced Cochrane review, but my approach is similar though the requirement for anticoagulants in these patients is less compelling.


Table. Summary of Placebo-Controlled Trials for Treatment of Superficial Thrombophlebitis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Comparator</th>
<th>No. of Studies</th>
<th>Symptomatic VTE RR (95% CI)</th>
<th>Extension of ST RR (95% CI)</th>
<th>GRADE Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fondaparinux 2.5 mg sc daily × 45 d</td>
<td>Placebo</td>
<td>1 (n = 3,002)</td>
<td>0.15 (0.04-0.50)</td>
<td>0.08 (0.03-0.22)</td>
<td>Moderate</td>
</tr>
<tr>
<td>LMWH prophylactic dose × 8-12 d</td>
<td>Placebo</td>
<td>1 (n = 222)</td>
<td>1.22 (0.38-3.89)</td>
<td>0.44 (0.26-0.74)</td>
<td>Low</td>
</tr>
<tr>
<td>LMWH therapeutic dose × 8-12 d</td>
<td>Placebo</td>
<td>1 (n = 222)</td>
<td>0.85 (0.23-3.06)</td>
<td>0.46 (0.27-0.77)</td>
<td>Low</td>
</tr>
<tr>
<td>NSAIADs</td>
<td>Placebo</td>
<td>1 (n = 211)</td>
<td>0.91 (0.25-3.82)</td>
<td>0.46 (0.27-0.78)</td>
<td>Low</td>
</tr>
</tbody>
</table>

Abbreviations: LMWH, low-molecular-weight heparin; RR, relative risk; sc, subcutaneously; VTE, venous thromboembolism.*Also included recurrent superficial thrombophlebitis.

LORI-ANN LINKINS, MD
Dr. Linkins has received payment for data adjudication of the MARINER trial (rivaroxaban for prophylaxis in medical patients).

Seeking Insight into the AML Subpopulations and Microenvironment Through Single-cell RNA-Seq


The most recent World Health Organization and European Leukemia Network classification systems use somatic and molecular findings to distribute cases of acute myeloid leukemia (AML) into favorable, intermediate, or adverse risk categories, which in turn influence treatment strategies for patients.1,2 Despite advances in treatment stratification, relapse after initial remission is common in all categories, and a subset of patients also remain refractory to induction chemotherapy. This has led to an interest in better understanding tumor biology to inform development of novel therapies, with a resultant resurgence of interest in transcriptionomics. The current mutation literature has shown that heterogeneity within tumors plays an important role in recurrence and resistance.3 However, comprehensive molecular profiling in AML that includes transcriptionomics has not yet been widely adopted despite the publication of several AML risk stratification models that incorporate combinations of somatic mutations, gene expression, and clonality.4,5 These prior studies used various methods of assessing gene expression profiles of entire AML samples without single-cell resolution.

In their recent article, Dr. Peter van Galen and colleagues used tandem single-cell transcriptomics and genotyping to assess bone marrow (BM) monoclonal cells from 16 patients with AML at diagnosis and during treatment, and BM aspirates from five healthy donors.6,7 Using the high-resolution single-cell technology, the study published high-throughput single-cell RNA sequencing (scRNA-seq) as well as single-cell genotyping by short-read and long-read sequencing to detect and phase AML mutations in individual cells. A machine learning classifier distinguished malignant cells from normal cells based on mutation status and classified cell types on the hematopoietic stem cell to myeloid differentiation (HSC to MDS) axis as well as their similarity to normal BM cell types. The analysis revealed six distinct malignant AML cell phenotypes within the AML cases. The proportion of these cell types varied across the AML cases studied as well as over the course of the 5 years for each AML. The gene signature profiles of these six cell phenotypes were used to score bulk expression profiles of 179 diagnostic AML aspirates from the Cancer Genome Atlas (TCGA). The TCGA cohort could be clustered into seven different malignant cell composition profile groups that, not surprisingly, demonstrated correlation with both characteristic genetic lesions (i.e., acute promyelocytic leukemia mapped to a high granulocyte-macrophage progenitor signature while CBFB-MYH11 type cases mapped to high monocytes and dendritic cell-like) and former French–American–British morphologic subtypes. Additionally, maturation dysynchrony was found by transcriptional profiling that is reminiscent of the aberrant immunophenotypes of leukemic blasts and maturing cells seen typically by flow cytometry.

Interestingly, within the somatic mutation subtypes, the investigators found differential behavior between NPM1 subgroups— one with a strong HSC/progenitor phenotype in cases with co-occurring NPM1 and FLT3-ITD mutations and a second with a more differentiated monocyte- to dendritic cell-like signatures with IDT-negative cases. Even within the FLT3 mutated cases, different cellular lineages were identified. Genotyping of one case showed three subclones: “A” with a FLT3 p.A680V mutation, “B” with an additional FLT3-ITD mutation on the opposite allele, and “C” with a FLT3 p.N841K mutation only. Interestingly, most cells in subclones “A” and “B” expressed signature genes associated with progenitor-like cells, and the majority of subclone “C” cells expressed genes associated with differentiated monocyte-like or conventional dendritic-like cells. In these examples, the more progenitor-like phenotype typically was associated with an advanced prognosis.

Another area of recent investigative interest has been the study of antitumor immune responses within AML. Although therapeutic trials of immunomodulating treatments in AML have been limited to date, findings have indicated a role of T cells in the regulation of impairing anti-leukemic immune responses.8 Dr. Van Galen and colleagues also looked at the T cell signatures in the AML and control samples. They found that AML BMs contained fewer T cells and cytotoxic T lymphocytes but relatively more T regulatory cells (also confirmed by immunohistochemical analysis of CD25 and FOXP3). Additionally, the investigators performed in vitro assays of T cell activation that showed a strong inhibitory effect associated with the presence of leukemic cells from an acute

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Dr. DeZern indicated no relevant conflicts of interest.

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myeloid leukemia cell line, MUTZ-3. Cultures enriched with monocyte-like (CD14+ MUTZ-3) cells were also particularly suppressive of T cell activation, decreasing T cell activation by 10-fold (p<0.0001). Review of the transcriptome data from the AML cases in this series showed that monocyte-like AML cells preferentially expressed genes that inhibit immune response to AML and different T cell subset distributions in AML, paving the way for future studies observing immunosuppression in AML. Despite these findings and several other gene expression profiling AML stratification models,1 transcriptions has yet to find a place in routine clinical practice. Additional work is needed to parse out the clinical interplay between more traditional prognostic markers and the adverse prognosis associated with progenitor-like signatures in clonal and subclonal populations, the effect of immunosuppressive monocytes, and the T cell subset milieu. Additionally, by using the presence of mutations, including genes such as DNMT3A and TET2, to distinguish the malignant clonal cells from the background normal cells, the authors did not discriminate between clonal hematopoiesis and leukemic hematopoiesis. These complexities will require further elucidation prior to clinical adoption. However, it is clear that the use of single-cell profiling provides the added granularity needed to take our understanding of AML biology to the next level.


3. Welch JS, Ley TJ, Link DC, et al. The origin and evolution of mutations in DNMT3A using the presence of mutations, including genes such as DNMT3A and TET2, to distinguish the malignant clonal cells from the background normal cells, the authors did not discriminate between clonal hematopoiesis and leukemic hematopoiesis. These complexities will require further elucidation prior to clinical adoption. However, it is clear that the use of single-cell profiling provides the added granularity needed to take our understanding of AML biology to the next level.


PET-adapted Strategies in Advanced Stage Hodgkin Lymphoma: Big to Small, or Small to Big, or Does It Even Matter?


The preferred treatment for advanced-stage Hodgkin lymphoma (HL) has historically differed with geography, with oncologists in the United States favoring chemotherapy with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), whereas Europeans have favored escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone). ABVD is associated with an inferior progression-free survival (PFS), but its proponents argue that 1) this decrement in PFS is less important than the increase in toxicity, including serious infection, infertility, and secondary malignancies, seen with escalated BEACOPP and 2) there is no overall survival (OS) benefit attached to the more toxic regimen. In an attempt to avoid excessive toxicity in patients their therapy intensified to ABVD or escalated BEACOPP, they used radiation therapy to intensified to ABVD or escalated BEACOPP, they used radiation therapy to.

In the AHL2011 study, reviewed here in the context of the existing literature, all patients with advanced-stage HL were randomized to standard treatment (n=413) consisting of six cycles of escalated BEACOPP, or to PET-driven treatment (n=410) where the results of PET2 were used to determine subsequent therapy. PET2-negative patients (Deauville 1 or 2) received additional escalated BEACOPP and PET2-negative patients (Deauville 3–5) received ABVD. PET2-positive patients (Deauville 3–5) were then randomized to receive ABVD or bleomycin removal from subsequent cycles (RATHL). With this strategy, two- and three-year PFS rates for patients on the SWOG S0816 and RATHL trials overall were 79 percent and 67 percent, respectively. Dr. Rene-Olivier Casanovas and colleagues reported the opposite strategy in Lancet Oncology this year; they discussed treatment de-escalation based on a reassuring PET response after two cycles of escalated BEACOPP in an attempt to limit toxicity in patients for whom it is not needed.

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A new multicenter study challenges dogma of normal saline boluses (NSBs) to treat acute vaso-occlusive pain in sickle cell disease (SCD).

When I come home from the hospital my legs are very swollen… and they hurt… I gain 10+ pounds and it takes over two weeks for my legs to get back to their normal size… This scenario has been retold to me repeatedly by my patients with SCD. So much so that I have adjusted my usual practice of liberal hydration during acute pain to one of limited hydration with hypertonic fluids for 24 to 48 hours at no more than maintenance fluids. In my review of the literature to support my practice, I noted that the use of intravenous hypertonic fluid had become the community standard for supportive management of acute vaso-occlusive episodes (VOEs) in SCD in addition to parental analgesics, with little supportive evidence. Supplemental hydration is routinely used regardless of the hydration state of the individual patient, with little consistency in the amount, type, and rate of administration.3 The proposed rationale for supplemental hydration (typical with saline) during sickle VOEs is based somewhat on the known molecular mechanisms that trigger erythrocyte sickling and precipitate vaso-occlusion.4 This surmises that a logical approach to treating acute VOEs should include avoiding or inhibiting the predisposing factors that result in the intermolecular interactions that favor sickling, specifically fewer (infection) acidosis, and hypoxia. Individuals with SCD are believed to be predisposed to dehydrated due to increased skin water loss and reduced fluid intake during acute illness, and polycythemia from hypothermia.5-9 It has thus been proposed that dehydration provokes sickling via circulatory stagnation that leads to increased blood viscosity, hypoxia, and eventually acidosis, and that this acidosis can be exacerbated during episodes of febrile illness and infections.

A much less well-touted mechanism responsible for initiating and perpetuating the sickling of erythrocytes is intracellular dehydration. Perhaps the SCD patient should shift toward interventions that result in reconverting the red cell rather than increasing intravascular plasma volume with NSB. Furthermore, rehydration using hypertonic fluids (normal saline) may be expected to only have an impact on increasing intravascular volume and vasodilation and do very little to rehydrate the sickle erythrocyte.10

The Saline Against Lactated Ringers or Plasma-Lyte in the Emergency Department (SALT-ED) trial and the Isotonic Solutions and Major Adverse Renal Events Trial (SMART) both suggest that giving balanced crystalloids rather than an acute resuscitation fluid with lower ion concentration (e.g., lactated Ringers or plasma-lyte) during lower incidence of adverse kidney events within 30 days compared to saline (4.7% vs. 5.6%; adjusted odds ratio, 0.82; 95% CI, 0.70-0.95; p=0.01).11

Recently, investigators challenged the dogma of giving NSBs as part of acute SCD management, which is recommended practice in most emergency departments (EDs). Using microfluid in vitro models of the post capillary bed circulation, Dr. Marcus A. Carden and colleagues demonstrated that exposing sickle red blood cells (RBCs) to hypertonic solutions reduced erythrocyte deformability and increased needed vaso-occlusal pressure associated with normocytic fluids.5 This provided clinical rationale to investigate the clinical impact of NSB on pain outcomes in patients with SCD. They then conducted a rigorously designed multi-institution retrospective cohort study of the use of supplemental hypertonic fluids for acute and chronic pain in 400 children (mean age: 13.8 ± 4.9 years) with SCD. Not surprisingly the majority (66%) of patients received a fluid bolus (despite no signs and symptoms of dehydration), with hypertonic normal saline almost exclusively (99.2%) representing the fluid choice. Of the choice, average volume infused during the ED stay was 18.2 ± 9.5 ml/kg. Patients who received an NSB had similar pre-illness pain scores and similar overall opioid consumption compared with those who did receive an NSB. However, they experienced less post-illness pain scores (p<0.001), spent more time in the ED (p=0.01), and had higher rates of admission (p=0.01). Due to the significant negative association of NSB with acute pain outcomes reported in a prior single-institution report11 and is supported by findings in non-SCD cohorts, investigators concluded that the routine use of NSB in SCD patients without clear indication of dehydration is not indicated.

So, why is it so easy to stick to the “tradition” of hydrating patients with SCD using NSB despite no evidence to support this practice, even in the absence of dehydration? There has hitherto been lack of evidence to support use of NSB in euveolic patients with VOEs, and yet it remains common practice in most pediatric EDs.

While the study by Dr. Carden and colleagues was limited by its retrospective cohort design, it does provide strong rationale for more research to determine the appropriate type of intravenous fluids to use in acute pain management in SCD. More physiologic, balanced salt solutions may be better for our patients with SCD given their unique red cell physiology as these are more likely to promote red cell rehydration by driving K+ and water into the RBC. Perhaps my anecdotal practice of limited hyperosmolar fluids is indeed does provide strong rationale for more research to determine the appropriate type of intravenous fluids to use in acute pain management in SCD.

Most end-stage myeloma cells are short-lived, terminally differentiated plasma B cells. Therefore, as is the case for many clonal cancers, tumor stem cells (CSCs) or in this case myeloma stem cells (MMSCs) have been implicated in disease progression. Although the concept of CSC has been around for decades, CSCs were only definitively described in 1997 in acute myeloid leukemias.2 Since that time, this population has been identified in many solid and hematologic malignancies. Mark W. Smalley and colleagues have been used to identify MMSCs, including side population and aldehyde dehydrogenase (ALDH) activity. Side population cells were first identified in murine BM with the ability to self-renew and differentiate into predominantly myeloma clones that constitute the lesion. Conceptually, a proper CSC assay should evaluate whether a population can propagate malignant clones indefinitely and in the setting of disease dissection. Conversely, ALDH has been shown to be highly expressed in primitive hematopoietic stem cells and showed increased activity in CSCs purified from various solid and hematopoietic cancers.12 However, the identification of MMSCs should rely on phenotype rather than CSC characteristics. In that regard, MMSCs can be defined as a cell in the malignant tissue that serves as a biomarker for progression from premalignant monoclonal gammopathy of undetermined significance (MGUS) to overt MM. Although this XBP1+ transgenic XBP1-Ig transgenic model has been reported as a recapitulation of clinic developmental stages of MGUS to MM, no detailed analysis of the B-cell compartment has been performed.

In this study, Dr. Joshua Kelner and colleagues investigated the kinetics of B-cell development in XBP1-Ig mice and found that B-cells are post-germinal center, class-switched B cells (B220+CD19+IgM+IgD), transitional plasmablasts (CD19+B220+IgM+IgD), and plasma cells (CD138+). Based on surface (sIgA) and cytoplasmic (cIgM, cIgD) expression of membrane and granularity, these MMPCs can be further divided into PC progenitor cells (PCPCs; sIgA+IgM+IgD+), B-cell progenitor cells (BPCs; sIgA+AA4.1+IgD+), and plasma cells (PC; sIgA+AA4.1+IgD+). These authors then comprehensively examined the expression of MM/BCPC/PCPC transcription factors, expression of adhesion molecules, antigen specificity, morphology, stem/progenitor/mature characteristics, and ability to differentiate to myeloma cells in vivo.

As expected, BCPCs express high levels of Pax9, a transcription factor important for maintaining B cell phenotype and preventing plasma cell formation. Similarly, PCs express high levels of both B220 and B220, but only intermediate levels of B220, suggesting a transitional state between BCPC and PC. The authors thus used these markers to examine the specificities of these subpopulations. HSA-specific memory B cell, a positive control, captured both populations, whereas sIgM+IgD+PCs (a negative control) expressed a single institution report11 and is supported by findings in non-SCD cohorts, investigators concluded that the routine use of NSB in SCD patients without clear indication of dehydration is not indicated.

So, why is it so easy to stick to the “tradition” of hydrating patients with SCD using NSB despite no evidence to support this practice, even in the absence of dehydration? There has hitherto been lack of evidence to support use of NSB in euveolic patients with VOEs, and yet it remains common practice in most pediatric EDs.

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Acute DVT or PE in Cancer Patients: Apixaban Reasonable to Use?

**STUDY TITLE:** Apixaban for the Treatment of Venous Thromboembolism in Patients With Cancer: A Prospective Randomized Open Blinded End-Point (Probe) Study (CARAVAGGIO)

**CLINICALTRIALS.GOV IDENTIFIER:** NCT03045406

**PARTICIPATING CENTERS:** Multicenter, international study under the leadership of Dr. G. Agnelli, of the University of Padova in Italy

**ACCRUAL GOAL:** 1,168. As of May 21, 2019, 1,115 patients have been randomized worldwide.

**STUDY DESIGN:** This is an open-label randomized treatment trial. Individuals on the experimental arm receive oral apixaban, 10 mg twice daily for seven days, after which they are transitioned to dosing once daily (total treatment period, 6 months). Subjects on the active comparator arm receive dalteparin, 200 IU/kg subcutaneously once daily for one month, and thereafter, 150 IU/kg once daily for five months. The primary outcome is recurrent venous thromboembolism (VTE) during six months on the trial. Patients are eligible if they have 1) newly diagnosed, objectively confirmed symptomatic or unsuspected proximal deep venous thrombosis (DVT) or symptomatic pulmonary embolism (PE), or unsuspected PE in a segmental or more proximal pulmonary artery, and 2) any type of cancer (other than basal-cell or squamous-cell carcinoma of the skin, primary brain tumor or intracerebral metastasis, and acute leukemia). Exclusion criteria include poor Eastern Cooperative Oncology Group (ECOG) Performance Status (grade 3 or 4), life expectancy of less than six months, active bleeding, or clinically significant bleeding that contraindicates anticoagulation; and thrombocytopeny, venous catheter insertion, or thrombolyis used to manage the current episode. Sponsor is the Fondo Ricerca (Federation of the Associations of Internist Hospital Managers, www.fadis.org/it), an Italian internal medicine society, and the University of Perugia, Italy.

**RATIONALE:** Based on somewhat dated society guidelines from 2015 to 2016, a low-molecular-weight heparin (LMWH) is still the gold standard treatment for patients with cancer who have VTE. A new American Society of Clinical Oncology cancer guideline is expected to be published soon, and based on recent clinical trial data of the studies listed in the table, it may well list edoxaban and rivaroxaban together with LMWH as treatment options preferred over vitamin K antagonist therapy in patients with cancer and acute VTE. Given the inconvenience of subcutaneous injections and the cost of LMWH, the question that many oncologists have is whether the results of these large trials are generalizable to all cancer patients. The next-generation sequencing (NGS) platform will establish whether FLT3 inhibition in this setting can generate helpful data for physicians and patients. It is accruing well and on track to complete enrollment within 24 months.

**STUDY DESIGN:** This trial is enrolling adult patients with FMS-like tyrosine kinase 3 (FLT3)/internal tandem duplication (ITD)/ITD-mutated acute myeloid leukemia (AML) in first morphologic complete remission (CR1), as defined by < 5% blasts in the bone marrow (BM) with no morphologic characteristics of acute leukemia, in marrow with no evidence of extramedullary disease) who undergo allogeneic hematopoietic cell transplantation (HCT). This is a double-blind, placebo-controlled, randomized, multi-center phase III trial in which participants are randomized to receive gilteritinib or placebo beginning after the time of engraftment, for two-year period. Participants are stratified according to three factors: 1) conditioning regimen intensity (myeloablative vs. reduced intensity/ nonmyeloablative), 2) time from first day of hematopoietic cell infusion to randomization (30-60 days vs. 61-90 days) and 3) presence versus absence of or unknown minimal residual disease (MRD) from a preregistration BM aspirate. The primary objective is to compare relapse-free survival (RFS) between the arms at two years.

**RATIONALE:** FLT3 is a common mutation seen in approximately 30% of AML cases. It usually presents with proliferative white blood cell counts, often in younger patients. These patients are at high risk of relapse even if they achieve a remission. There is an increased chance of achieving CR1 with administrations of FLT3 tyrosine kinase inhibitors (TKIs) in induction or at relapse as well as to pursue a potential cure with HCT. The current BMTCTN 1506 trial is well-positioned to evaluate the impact of maintenance therapy with gilteritinib on the RFS of participants with FLT3/ITD AML who have successfully undergone allogeneic transplantation. A dose of 120 mg of gilteritinib will be given orally daily for seven days, after which the dose will be reduced to 80 mg daily for 21 days. The CARAVAGGIO study started enrollment in August 2018, and the study will continue enrolling participants worldwide. Enrollment is expected to finish at the end of May 2019, and follow-up of the last patient enrolled will end six months later, around November 2019. This study, like the HOKUSAI trial, is well designed and of sufficient size to provide solid data on the efficacy and safety of allogeneic in patients with acute myeloid leukemia (AML).

**COMMENT:** The CARAVAGGIO Study started enrollment in August 2018, with a target enrollment number of 1,168. As of May 21, 2019, 1,135 patients have been randomized worldwide. Enrollment is expected to finish at the end of May 2019, and follow-up of the last patient enrolled will end six months later, around November 2019. This study, like the HOKUSAI trial, is well designed and of sufficient size to provide solid data on the efficacy and safety of allogeneic in patients with acute myeloid leukemia (AML). While numerous oncologists have already switched from using LMWH to rivaroxaban or apixaban, this switch has occurred with only limited data to support the use of apixaban in this setting. However, a larger, more definitive study of a size similar to the HOKUSAI trial, a lower risk of recurrent VTE with rivaroxaban, but at the cost of more clinically relevant nonmajor bleeding.

**Editors’ Choice**

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

**APRIL 11, 2019**


This article presents novel insights into the pathogenesis of bone marrow fibrosis in JAK/STAT-driven myeloproliferative neoplasia. Drawing on a series of elegant experiments in mouse models, the investigators provide compelling evidence for the critical role of the nuclear vitamin D receptor and bone marrow macrophages in the pathogenesis of idiopathic myelofibrosis.

**APRIL 18, 2019**


**APRIL 25, 2019**


and


Investigators using complementary approaches report critical insights into the structure and function of ADAMTS13. Their studies reveal interactions that allosterically regulate the proteolytic activity of ADAMTS13 on von Willebrand factor.

**MAY 2, 2019**


Dr. Miguel Ganuza and colleagues examine whether steady-state hematopoiesis in the aging mouse displays a decline in clonal complexity reflecting human clonal hematopoiesis of indeterminate potential (CHIP). As with human hematopoietic stem cells, they demonstrate loss of heterogeneity and myeloid skewing, but studies implicate gene mutations different from those in humans.

**MAY 9, 2019**


In a plenary paper, the investigators demonstrate that megakaryocytes, mainly recognized for their role in the generation of platelets, are also capable of preventing the spread of viral infection, indicating a role in immunity.

**MAY 13, 2019**


After nearly four years of follow-up, the authors present impressive sustained, progression-free, and overall survival benefits following the use of the Bruton tyrosine kinase inhibitor ibrutinib in patients with high-risk relapsed or refractory chronic lymphocytic leukemia.

**MAY 20, 2019**

Alvarado LJ, Huntsman HD, Cheng H, et al. Eltrombopag maintains human hematopoietic stem and progenitor cell functionally inactive. Using mouse models of hemophilia B, Dr. Brian Cooley and colleagues demonstrated that this circulating species impacts response to FIX prophylaxis, perhaps explaining the wide range of individual responses to infused FIX products in patients with hemophilia B.

Dr. Moll has been a consultant for Janssen. Dr. Nagler has no relevant conflicts of interest.

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Table: Cancer and VTE: Prospective Randomized DOAC Trials

<table>
<thead>
<tr>
<th>Completed</th>
<th>Trial Name</th>
<th>New Drug</th>
<th>Comparator</th>
<th>N</th>
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<tbody>
<tr>
<td>HOKUSAI</td>
<td>Edoxaban</td>
<td>Dalteparin</td>
<td>1,046</td>
<td>Raschke GE et al</td>
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<tr>
<td>SELECT-D</td>
<td>Rivaroxaban</td>
<td>Dalteparin</td>
<td>406</td>
<td>Young AM et al</td>
</tr>
<tr>
<td>ADAM</td>
<td>Apixaban</td>
<td>Dalteparin</td>
<td>300</td>
<td>McBane RD et al</td>
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<table>
<thead>
<tr>
<th>Ongoing</th>
<th>Trial Name</th>
<th>New Drug</th>
<th>Comparator</th>
<th>N</th>
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</thead>
<tbody>
<tr>
<td>CARAVAGGIO</td>
<td>Apixaban</td>
<td>Dalteparin</td>
<td>1,168*</td>
<td>Study ongoing. First results expected at the end of 2019.</td>
</tr>
</tbody>
</table>

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*1,135 patients enrolled as of May 21, 2019.
A Woman With Thrombocytopenia Status Post–Partial Gastroctomy

MARYAM ASIF, MD,1 KYLE PARKER, MD,2 AND FATIMA ALDARWEESH, MD3
1. Pathology Resident, University of Chicago, Chicago, IL
2. Resident Pathologist, University of Chicago Medical Center, Chicago, IL
3. Assistant Professor, Associate Medical Director of Blood Bank and Transfusion Service, University of Chicago, Chicago, IL

A 62-year-old woman presented to the emergency department with abdominal pain and weakness; she has a medical history significant for end-stage renal disease secondary to focal segmental glomerulonephritis status after directed donor kidney transplantation two years ago. A computed tomography (CT) scan revealed pneumoperitoneum. She emergently underwent exploratory laparotomy with distal gastrectomy and gastrojejunostomy.

Upon admission, her platelet count was 96 × 10^3/µL (reference range [RR], 150-450 × 10^3/µL), approximately five days post-surgery her mental status waned, and platelet count decreased to 9 × 10^3/µL.

Other notable tests produced the following results:

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>8.0</td>
<td>11.5-15.5</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>3.6</td>
<td>0.5-1.4 (baseline, 3.4)</td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/L)</td>
<td>1,280</td>
<td>116-245</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>2.3</td>
<td>0.9-1.1</td>
</tr>
<tr>
<td>Mean corpuscular volume (fL)</td>
<td>87</td>
<td>81-99</td>
</tr>
<tr>
<td>Haptoglobin (mg/dL)</td>
<td>&lt; 20</td>
<td>51-192</td>
</tr>
<tr>
<td>D-dimer (µg/mL)</td>
<td>&gt; 20</td>
<td>&lt; 0.40</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>7.2</td>
<td>0.1-1.0</td>
</tr>
<tr>
<td>Unconjugated bilirubin (mg/dL)</td>
<td>2.7</td>
<td>0.1-1.0</td>
</tr>
<tr>
<td>Conjugated bilirubin (mg/dL)</td>
<td>4.5</td>
<td>0-0.3</td>
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<tr>
<td>Tacrolimus level (ng/mL)</td>
<td>20.8</td>
<td>5-20</td>
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<tr>
<td>ADAMTS13 functional level</td>
<td>24%</td>
<td>69-133%</td>
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<tr>
<td>ADAMTS13 inhibitor</td>
<td>&lt; 0.5</td>
<td>&lt; 0.5</td>
</tr>
<tr>
<td>C3 complement level (mg/dL)</td>
<td>78</td>
<td>83-188</td>
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<tr>
<td>C4 complement level (mg/dL)</td>
<td>12</td>
<td>18-45</td>
</tr>
<tr>
<td>PF4 ELISA (OD)</td>
<td>0.152</td>
<td>&lt; 0.4</td>
</tr>
</tbody>
</table>

Abbreviations: ADAMTS13, A disintegrin and metalloproteinase with thrombospondin-1–like domains 13; ELISA, enzyme-linked immunosorbent assay.

What is the diagnosis?
A. Thrombotic microangiopathy, thrombotic thrombocytopenia purpura
B. Thrombotic microangiopathy, other
C. Heparin-induced thrombocytopenia
D. Antibody-mediated renal allograft rejection

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

Drs. Asif, Parker, and Aldarweesh indicated no relevant conflicts of interest.