ASH NEWS AND REPORTS

Circulating Tumor DNA in Lymphoma Monitoring: Fantasy, Fad, or Fact?

Although monitoring of select protein biomarkers has long been an integral part of standard oncology care (e.g., prostate-specific antigen or carcinoembryonic antigen), methods with sufficient analytical sensitivity to enable detection of rare tumor-associated variants from circulating tumor DNA (ctDNA) are now available. These methods have gained a critical place in solid tumor variant identification and monitoring and are now increasingly being applied to lymphomas. Historically, radiologic methods have been the standard of care for monitoring lymphoma responses to therapy (specifically positron emission tomography combined with computed tomography [PET/CT]), with histologic confirmation required in some circumstances. However, both histology and PET/CT are challenging in certain lymphoma types, especially classic Hodgkin lymphoma (cHL).

The initial application of ctDNA in lymphoma care was in the monitoring of clonotypic immunoglobulin gene rearrangements in diffuse large B-cell lymphoma (DLBCL) with a specificity of 100 percent (i.e., no false positives), versus only 56 percent for PET/CT.1,2 Subsequent studies introduced the use of somatic tumor variants for this purpose.3,4 Now, Drs. Valeria Spina and Alessio Bruscaiggion and colleagues have demonstrated the utility of this method in cHL. Since prior studies were all performed on tumors with diffuse involvement by large numbers of lymphoma cells, the validity of this approach in a tumor type with rare neoplastic cell clusters and infiltrative inflammatory background is even more astounding. Drs. Spina and Bruscaiggion’s study makes several key points, as outlined in the following sections.

cDNA identifies tumor-specific variants in cHL. Mutations identified in the ctDNA were compared to paired tumor gDNA, with 87.5 percent detection in ctDNA of variants identified in the tumor. None of these variants were detected in paired tumor background tissue without neoplastic cells, confirming their origin in the neoplastic cells. Additionally, all germline variants were excluded through comparison with paired normal gDNA from granulocytes. Additional variants found in ctDNA and not in the tumor (106 in ctDNA vs. 96 from tumor gDNA) tracked with disease status, confirming their assessment of neoplasia. Overall, somatic mutations were identified in 81.2 percent of cHL cases, with a mean of five mutations per case.

cDNA tracks with tumor burden in cHL. The average variant allele fraction (VAF) was 5.5 percent, with most variants found at a VAF greater than 1 percent. Summing the ctDNA burden, there was correlation between the ctDNA load and Ann Arbor stage I versus stages II to IV (P = 0.021), limited (IA, IB, or IIA without bulky disease) versus advanced.

The Case
A 22-year-old man with no significant prior medical history presented to his local clinic with a two-month history of maculopapular skin lesions. A lesion noted on the face adjacent to his nose was non-pruritic and had a purplish discoloration. Several other lesions appeared in subsequent weeks, and the patient was seen by his local primary care team. He had no fevers, night sweats, or weight loss. Results from both standard complete blood count and chemistry panel were within normal ranges (no circulating blasts, no liver/kidney abnormalities, adequate albumin level). He had no significant past medical history and was a non-smoker. The patient had a history of a minor cut on his leg that he did not recall getting infected. The patient worked as a butcher and had been exposed to fresh meat and fish. His ECOG performance status was 1. The patient was referred to an dermatology fellow who performed a skin biopsy on a lesion on the patient’s right upper arm and submitted it to the pathology lab.

A few weeks later, the dermatology fellow called the patient and told him that he needed to come back to the clinic because he needed to do a skin biopsy on the patient’s right upper arm. When the patient returned to the clinic, the skin lesions had not resolved, with several more appearing in the trunk. The patient was seen by his local primary care team. He had no fevers, night sweats, or weight loss. Results from both standard complete blood count and chemistry panel were within normal ranges (no circulating blasts, no liver/kidney abnormalities, adequate albumin level). He had no significant past medical history and was a non-smoker. The patient had a history of a minor cut on his leg that he did not recall getting infected. The patient worked as a butcher and had been exposed to fresh meat and fish. His ECOG performance status was 1. The patient was referred to an dermatology fellow who performed a skin biopsy on a lesion on the patient’s right upper arm and submitted it to the pathology lab. The next day, the patient was called back to the clinic by the dermatology fellow and told him that he needed to come back to the clinic because he needed to do a skin biopsy on the patient’s right upper arm. When the patient returned to the clinic, the skin lesions had not resolved, with several more appearing in the trunk. The patient was seen by his local primary care team. He had no fevers, night sweats, or weight loss. Results from both standard complete blood count and chemistry panel were within normal ranges (no circulating blasts, no liver/kidney abnormalities, adequate albumin level). He had no significant past medical history and was a non-smoker. The patient had a history of a minor cut on his leg that he did not recall getting infected. The patient worked as a butcher and had been exposed to fresh meat and fish. His ECOG performance status was 1. The patient was referred to an dermatology fellow who performed a skin biopsy on a lesion on the patient’s right upper arm and submitted it to the pathology lab. The next day, the patient was called back to the clinic by the dermatology fellow and told him that he needed to come back to the clinic because he needed to do a skin biopsy on the patient’s right upper arm. When the patient returned to the clinic, the skin lesions had not resolved, with several more appearing in the trunk. The patient was seen by his local primary care team. He had no fevers, night sweats, or weight loss. Results from both standard complete blood count and chemistry panel were within normal ranges (no circulating blasts, no liver/kidney abnormalities, adequate albumin level). He had no significant past medical history and was a non-smoker. The patient had a history of a minor cut on his leg that he did not recall getting infected. The patient worked as a butcher and had been exposed to fresh meat and fish. His ECOG performance status was 1. The patient was referred to an dermatology fellow who performed a skin biopsy on a lesion on the patient’s right upper arm and submitted it to the pathology lab.

Patient Management
With its history of confusing nomenclature and diverse clinical manifestations, BPDCN has been a truly protein disease for pathologists and clinicians alike. While not the only hematologic malignancy to involve the skin, BPDCN is now recognized as one of the most common and most deadly blood-skin connecting cancers in this limited differential diagnosis space. Frequently, patients can present with skin-only disease, which can precede blood/marrow involvement, although blood/marrow involvement is now recognized as one of the most common and most deadly blood-skin connecting cancers. For this limited differential diagnosis space, frequently, patients can present with skin-only disease, which can precede blood/marrow involvement, although blood/marrow involvement is now recognized as one of the most common and most deadly blood-skin connecting cancers. In these three; bone marrow was ultimately positive for involvement (with flow and IHC demonstrating CD4, CD56, CD123, CD25, CD30, CD43, and CD45). A small subset of younger/healthy patients with BPDCN seem to benefit from stem cell transplantation (SCT), especially if done in first complete remission (CR1); however, this doesn’t apply to the majority of patients in our field, as the median age reported by most groups is 70 years and older.3,4 Therefore, new therapeutic approaches based on these scientific breakthroughs are sorely needed.

Fantasy, Fad, or Fact?
When asked what they believe the future holds for circulating tumor DNA in lymphoma monitoring, the hematology community had differing opinions. Some believe that circulating tumor DNA in lymphoma monitoring is a fad, while others believe that it is a fact. Still, others believe that it is a fantasy. The future of circulating tumor DNA in lymphoma monitoring remains to be seen.
Broadening the Focus on Global Sickle Cell Efforts

September is Sickle Cell Awareness Month, and in a President’s Column written earlier this year, I highlighted initiatives through which the Society can make a difference, including parts of the world where the sickle cell disease (SCD) burden is greatest. I wrote about ASH’s efforts to launch a global program that seeks to reduce SCD-related mortality by promoting newborn screening and early intervention in sub-Saharan African countries. While there is still much work to be done, I would like to share some updates with you, and in particular, tell you about a trip I took this summer to Ghana, where on behalf of ASH, I connected with individuals and institutions who share our hope that newborn screening for SCD will be transformational in sub-Saharan African populations, much as it has been in the United States.

Our first stop was in Kumasi, the second largest city in Ghana. The newborn screening program in Kumasi that was launched more than two decades ago as a feasibility pilot with funding from the National Heart, Lung, and Blood Institute, has now grown to a network of 21 governmental and 14 private institutions. I saw firsthand the almost seamless incorporation of heel-sticks and data collection into primary care immunization sessions, and coordination of routine care and education for children in SCD clinics. The scope of this program was impressive, and ASH hopes to learn more about how aspects of the work in Ghana might be replicated in other sub-Saharan African nations. Next, ASH held a two-day meeting in Accra with hematologists from Ghana, Nigeria, Tanzania, and Zambia, and international stakeholders from Canada and the United Kingdom, to further develop a consortium. Our long-term goal is to reduce childhood mortality rates for SCD in the most hard-hit populations by introducing standard-of-care practices for screening and early intervention therapies at participating institutions. We hope that this will gradually expand in scope to reach more babies, create a framework for optimizing care, and facilitate introduction of disease-modifying therapies.

In honor of World Sickle Cell Awareness Day, which took place on June 19th, the Society launched a public awareness campaign on SCD in Africa through the promotion of new multimedia resources. Two videos, which took the form of a short documentary produced by ASH and a public service announcement created by the SCD Coalition, target the general public to dispute common myths about the disease and spotlight SCD resources, spreading the message about the importance of newborn screening. I encourage you to visit the coalition website and view them (www.scdcoalition.org/priorities/global).

Lastly, ASH has worked with the SCD Coalition to publish the State of Sickle Cell 2018 Report Card. With input from individuals with SCD, health care providers, and global health leaders, the report card estimates progress made since 2016 in several key areas and identities areas where more can be done. There has been measurable interval progress in professional education, research, access to care, and global issues, yet opportunities to make greater strides remain.

I trust we can all agree that the time is right for action in SCD, and that ASH is currently well-positioned to make an impact by improving outcomes. We continue to advocate for innovative strategies and new therapeutic interventions to reduce SCD-related morbidity and mortality domestically, while extending our reach beyond our national borders to ensure that our global community also progresses.

This is a proud moment in ASH’s history, and I hope you will join me in applauding the many individuals who are working with us to make curing SCD a reality.

Sincerely,

Alexis A. Thompson, MD
2018 Honorable Award Winners

At each year’s ASH annual meeting, the Society bestows its most prestigious awards to those hematologists whose work has had a profound influence on the field. Read on to learn more about the awardees and their contributions to hematology.

**WHO:** Victor Hoffbrand, DM, FRCP, FMed Sci, University College London  
**WHAT:** Wallace H. Coulter Award for Lifetime Achievement in Hematology  
**WHERE:** Hall A/B, San Diego Convention Center

**WHY:** Dr. Hoffbrand is recognized for his seminal contributions to the fields of megaloblastic anemia, iron chelation, and malignant hematology, as well as his commitment to the mentoring of trainees and his significant contributions to hematology education.

**WORDS OF WISDOM:** “This specialty is the best for combining laboratory with clinical work, whether in clinical care or research. Hematology continues to lead other specialties in the prevention and cure of inherited and acquired diseases including neoplasia. Within the field, there are great opportunities to specialize in several areas but also to combine practice in all. It is a specialty where hard work and dedication are needed but the rewards gained in improving the quality of life and survival of patients are immense.”

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**WHO:** Ross L. Levine, MD, Memorial Sloan-Kettering Cancer Center and Weil Cornell Medical College  
**WHAT:** William Dameshek Prize  
**WHERE:** Hall A/B, San Diego Convention Center

**WHY:** Dr. Levine receives this award in recognition of his significant contributions to the field of leukemia and myelodysplastic syndromes. He is among the several investigators who have driven the paradigm shift of leukemia research from simple identification of genetic mutations to consideration of how other variants contribute to blood cancer.

**WORDS OF WISDOM:** “There has never been a better time to be in the hematology field. The key is to follow the question wherever it takes you, and to work with the best, nicest people you can find at every stage of your career.”

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**WHO:** Alan D. D’Andrea, MD, Harvard Medical School and Dana-Farber Cancer Institute  
**WHAT:** Ernest Beutler Lecture and Prize  
**WHERE:** Hall A/B, San Diego Convention Center

**WHY:** Dr. D’Andrea is recognized for his contributions to the study of inherited and acquired bone marrow failure syndromes. In his presentation, he will discuss his basic research in Fanconi anemia, a constitutional marrow failure syndrome.

**WORDS OF WISDOM:** “More than any other disease subspecialty, hematology has needed but the rewards gained in improving the quality of life and survival of patients are immense.”

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**WHO:** Neal S. Young, MD, National Institutes of Health  
**WHAT:** Ernest Beutler Lecture and Prize  
**WHERE:** Hall A/B, San Diego Convention Center

**WHY:** Dr. Young is being recognized for his contributions to the study of inherited and acquired bone marrow failure syndromes. In his presentation, he will describe advances in clinical and translation studies of acquired aplastic anemia.

**WORDS OF WISDOM:** “…Working in an exciting laboratory and actually discovering something, and observing as a student the evaluation, diagnosis, and treatment of blood diseases, especially acute leukemia … I think I understood then the several remarkable features of hematologic that have continued to appeal to me all of my career: the possibility of dramatic therapeutic interventions in extremely, often acutely ill patients; the ability to make a diagnosis quickly at the bedside and the microscope; and the ready availability of blood and marrow for research.”

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**WHO:** Brunangelo Falini, MD, University of Perugia and the Institute of Hematology and Bone Marrow Transplantation in Italy  
**WHAT:** Henry M. Stratton Medal  
**WHERE:** Hall A/B, San Diego Convention Center

**WHY:** Dr. Falini is recognized for his seminal contributions to the understanding of acute myeloid leukemia and hairy cell leukemia through his clinical research, as well as his work in the field of hybridoma technology.

**WORDS OF WISDOM:** “…I wouldn’t have been able to reach certain results without knowing about clinical, morphologic, and monoclonal antibody and genomic technologies. Thus, my advice to someone considering entering hematology is to try to integrate as many data as possible to better understand the complexity of hematologic malignancies and to possibly translate new findings from bench to bed. I also used to say to my students that passion, determination, and innovation play a very important role.”

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**WHO:** Freda K. Stevenson, DPhil, University of Southampton and Southampton University Hospitals, UK  
**WHAT:** Henry M. Stratton Medal  
**WHERE:** Hall A/B, San Diego Convention Center

**WHY:** Dr. Stevenson is being recognized for her innovative work in the biology of B-cell malignancies such as lymphoma and chronic lymphocytic leukemia.

**WORDS OF WISDOM:** “Hematology should be the best discipline to translate laboratory findings to the clinic. So, work in an institution where this is encouraged. Biology and the clinic have always been closely aligned in hematology, so check that the interchange between scientists’ and clinicians’ work. Then enjoy the revelations.”

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**WHO:** Connie J. Eaves, PhD, FRS (Canada), Corresponding FRS (Edinburgh), BC Cancer Agency and University of British Columbia  
**WHAT:** E. Donnell Thomas Lecture and Prize  
**WHERE:** Hall A/B, San Diego Convention Center

**WHO:** José A. López, MD, University of Washington  
**WHAT:** ASH Award for Leadership in Promoting Diversity  
**WHERE:** Hall A/B, San Diego Convention Center

**WHY:** Dr. López has worked tirelessly to ensure that diversity and inclusion are priorities in the field. He has a long history of participation in programs aimed at increasing the number of underrepresented minorities in medicine and hematology, having collaborated with medical schools in Mexico to host students for summer research electives, among other notable initiatives.

**WORDS OF WISDOM:** “My advice is for investigators, whether they be clinical or basic, and it is to study a problem carefully and then trust your instincts. Also, do things the way that makes the most sense to your way of thinking and looking at the world, not the way everyone else does them. And be persistent.”

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**WHO:** Cage S. Johnson, MD, University of Southern California  
**WHAT:** ASH Award for Leadership in Promoting Diversity  
**WHERE:** Hall A/B, San Diego Convention Center

**WHY:** Dr. Johnson is recognized for his work to ensure that diversity and inclusion are priorities in the field of hematology. As a founding member and former president of the EE Just Society, he has taken many young, underrepresented minorities under his wing, encouraging them to successfully pursue careers in hematology.

**WORDS OF WISDOM:** “First, be the best internist or pediatrician that you can be. Then pick an area where you can be the expert and read the 1,000 papers on that subject (and think about what they mean), so that you know more than anyone else. Afterwards you will have the confidence to interact with the clinical and research communities on that subject.”

[Cont. on page 6]
patients achieved a major response with one cycle of available drug, five of which were CRs.11 On this basis, we set out to conduct a larger multicenter clinical trial with multiple cycles of SL-401.22 As updated recently at the 2018 European Hematology Association Annual Congress, 45 patients treated in stages 1-3 (median age 70 years, range 22-84) achieved an ORR of 90 percent in the frontline setting at the target dose identified (12 μg/kg) on Days 1-5 of a 21-day cycle. Of patients in the frontline setting being bridged to SCT and a 69 percent ORR in the relapsed/refractory setting. Among 114 patients treated across all clinical trials with SL-401 as a single agent at 12 μg/kg/day dosing, the most notable safety signal was the occurrence of capillary leak syndrome (CLS), which constituted 20 percent of all adverse events at all grades. CLS was observed in the setting of patients and generally manageable with safety parameters in place; these consist of assessment of baseline heart and organ function and careful daily assessments of clinical parameters prior to each dose, including albumin levels, patient weight, renal function, and liver function. Now, with median follow-up of 13.8 months (range 0.3-7.4 months), the median OS has not yet been reached among frontline treated patients at 12 μg/kg/day dosing.23

Patient Disposition and Long-Term Follow-Up

Historically, we have treated younger patients with ALL-based chemotherapy such as hyper-EVAD. We reviewed cytotoxic chemotherapy options versus clinical trial options. After discussion about the natural history of BPDCL and M-CLL, Dr. Michaelis limited the criteria for the patient opted for clinical trial with frontline SL-401. He received a total of five cycles, achieved a CR, maintained fit performance status throughout, and saw resolution of his skin lesions, normalization of marrow studies, and resolution of enlarged lymph nodes. He had no major complications during therapy and was able to proceed to an allogeneic SCT in CR1. Post-SCT, he was monitored closely and experienced no grade 3-4 adverse events. At the one-year mark, the patient was noted to remain in CR1 and thriving. Indeed, based on an ORR of 90 percent and a 45 percent rate of proceeding to SCT in the frontline setting, if/when available, the SL-401 clinical trial has now become de facto frontline standard of care for patients with BPDCL.

Future Directions and Therapy Strategies

In terms of targeting CD123, an emerging area of research is yielding novel therapeutic approaches with monoclonal antibodies, bi-specific antibodies, immunotherapy, and CAR-T therapies.24 Moving beyond single-agent CD123, therapies other than CD123 or combinations with CD123 will represent the next era of research in BPDCL. Other therapy approaches based on newer gene signature studies or novel biological rationale include bortezomib,25 BCL-2 inhibitors,26 PI3K/AKT/mTOR inhibitors,27 and/or bromodomain inhibitors.28 For those patients who are able to, SCT still seems to be the best overall curative option as part of any therapy program (cytotoxic chemotherapy, immunotherapy, targeted therapy) given the poor durability in many patients treated with cytotoxic chemotherapy alone and still unknown long-term durability of targeted agents in BPDCL. Approaches in the SCT field besides allogeneic SCT in CRI will include further investigation of timing, intensity, and types of allogeneic SCT, particularly in older patients, investigation of maintenance therapies post-SCT and SCT.29,30 As well as more focus on autologous for some patients (perhaps skin-only, or older patients unfit for allogeneic SCT), as some studies have suggested long-term benefit in select patients.31


Dr. Pennmaru and Dr. Konopleva indicated that they have received research funding from, and/or consulted with, Stemline, Cellectis, Abbvie, ImmunoGen, Daichi Sankyo, Plexintron, and Novartis.
David-Zacharie Issom, born in Geneva, Switzerland, was diagnosed with sickle cell disease (SCD) as an infant. Today, he is working on his PhD in health informatics at the Division of Medical Information Sciences at the University of Geneva, where he also serves on the faculty of medicine. Mr. Issom advocates for people living with SCD in his home country and around the world, sharing his unique personal journey and his own experience learning to take control of the disease. He had a conversation with Dr. Julie Kanter, who serves as the Director of Sickle Cell Research at the Medical University of South Carolina, about current barriers to optimal care and the potential for future cures — cures that Mr. Issom himself is working to make a reality.

Dr. Julie Kanter: You are quite an advocate for yourself and for others, so we wanted to do this interview to learn a little more. When were you diagnosed with SCD?

David Issom: I was about 10 months old when I was diagnosed, my parents noticed that I was crying a lot and they didn’t know why. So I had a blood sample taken, and the lab analysis found some strange red blood cells. I was lucky because SCD was not prevalent at all in Switzerland 30 years ago — I was the first SCD patient born there, so it was a bit complicated in the beginning to get adequate care.

Dr. Kanter: They must have matched you with a physician, but I’ll bet that physician didn’t have much SCD experience.

David: They had no experience with SCD. They actually published papers where I was the case study.

Dr. Kanter: SCD is clearly not common in Switzerland. Even now, do they do newborn screening?

David: No because it is still too rare.

Dr. Kanter: Are there more people in your country living with the disease now?

David: Yes. In Geneva, there are approximately 60 adults and roughly the same number of children with SCD — about 150 people. In the whole of Switzerland we don’t know exactly because we don’t have any census data. According to my own investigation with doctors in Switzerland, there are about 400 patients, but this is an estimation; we don’t have clear data.

Dr. Kanter: When did you first meet someone else who had SCD?

David: I was around 10 years old when a cousin of mine was diagnosed with SCD, but with [hemoglobin] SC not SS, so she had mild symptoms; she was an adult at the time. After several years, when I was doing my masters thesis in Norway, I was able to find, locate and meet with other people with SCD there.

Dr. Kanter: That’s a long time to be somewhat “by yourself.”

David: Yes, it was; we are very scattered in Switzerland … and isolated.

Dr. Kanter: Do you have any siblings?

David: Yes, I have one sibling, who is a carrier.

Dr. Kanter: And did your parents know they were carriers of sickle cell trait?

David: No, and since they were coming from Africa, it was even less diagnosed there. They had no idea they had the trait; they didn’t know if their ancestors or others in their family had it, and if so, those individuals probably died very young and had no idea.

Dr. Kanter: What part of Africa were they from?

David: Cameroon.

Dr. Kanter: Since you were originally diagnosed, what kind of complications have you had and what treatments have you tried?

David: As far as complications, I have nearly everything. I didn’t experience priapism, stroke, or G6PD loss, but I had everything else — pain of course, leg ulcers, and any other complication you can think of. I was among the first to try hydroxyurea starting in 1997, but I didn’t have a good response to it. My side effects were dry skin, discolored skin, dry mouth, and fatigue. Every week I had to go for a blood test, and I didn’t have any reduction in pain symptoms, so we stopped the treatment. I did blood transfusions therapies with good results, but we decided to stop treatment and use it only when needed. For instance, when I had an leg ulcer we used it, as well as during a pain crisis. But I hadn’t had a major crisis for about 10 years now, I still have some manageable pains maybe once a year when I push a little too hard.

Dr. Kanter: That’s amazing! To what do you attribute that improvement?

Dave: Many things. I didn’t have any more [successful] treatment options so I left with only one choice — to find a new solution for myself. Either I would find something new or I would die because I was experiencing so many crises. I would have five or six per year, and they were quite severe. My doctor told me that they would only become more severe because my organs had become so diminished.

Dr. Kanter: I decided to take action to increase my self-awareness to understand what my [pain crisis] triggers might be. I decided to accept my disease because if you don’t accept it, you won’t take any action. I learned how to react when I would experience triggers, how to avoid those triggers, and how to be extremely aware of my environment and my body. I did a lot of experimentation to understand what worked best for me and what did not work, but the key was in extreme self-awareness and environmental awareness so that I could understand the best strategy to avoid my symptoms.

Dave: It didn’t work every time. Sometimes I still had crises. Luckily, however, I had support from family and friends, and with good health care, I was able to avoid visits to the intensive care unit.

Dr. Kanter: Do you take any medicines now?

Dave: Just folic acid … and pain medicine when I experience pain, but this is rare.

Dr. Kanter: It’s possible to avoid most crises, but not all of them because we can’t control our entire environment, but we can still alter it. Extreme self-awareness and environmental awareness has worked for me, and now the process is automatic, but it took years to learn to “automate” it in my brain, as well as lots of daily practice.

Dr. Kanter: Do you think this is something you can teach others — to have this same self-awareness?

Dave: Yes, and I already do so now when I coach patients and advise families for instance as part of the Swiss Patients Organization (www.suissedrepano.ch) or my other initiatives (www.coachdrepamo.com), to help them find new [treatment] strategies.

Dr. Kanter: To switch topics a bit, how did you decide on your current career path?

Dave: Working in health informatics was something I decided on maybe 20 years ago because I of course spent a lot of time in the hospital, and my mother was a nurse (a midwife). Through this I experienced both the patient side and the caregiver side. I also saw that health informatics was up and coming at the time, and I had always had an attraction to that field. So going into health informatics was a very early career decision, though it was not yet a specific field of study for it. I had to study information technology and engineering, some medicine, and finally health informatics once it became available — first in Switzerland and then in Sweden. In Norway because they were quite advanced on these issues compared to the rest of the world.

Dr. Kanter: What taught you to be such a great advocate for yourself and want to “be better”?

Dave: I think we have room for improvement [in SCD]. In my daily life I have encountered many injustices. For instance, some health care providers have not always listened to me or trusted my stories or my requests. There are many cases where [physicians] see SCD patients as drug seekers. There is a great deal of stigma, and this led me to become more assertive and to learn how to talk to medical providers to help them reach out where they can and communicate better with patients. This helps us to receive the care that we need, and it also helps providers.

The injustices I have lived through (and I am not the only one) have helped me to become more knowledgeable and communicative. I had to understand the disease and to use the same words as a medical doctor to be more precise. It was worth it to be able to build my credibility. It was also pure survival — there were times I have been nearly killed by a medication. During my last crisis, I had a doctor who was taking care of me who would not give me the pain medication doses I required … they provided me with an overdose of ketamine, which led to respiratory arrest. It wasn’t the first time, but because the mind is powerful, I was able to force myself to breathe in and out and stay alive.

Dr. Kanter: That doctors do not know much about SCD is a huge problem everywhere, and many patients I treat also struggle with how to have a life while managing their disease. As their doctor, how do you think I should talk with them in a way that encourages them?

Dave: Let them know that there is no reason for them to think that they themselves are not “enough.” We are all humans with the same basic abilities and fundamentals, and with love and positivity, we can accomplish anything we want. If what we want to do is positive, I think nothing can stop us. But (and this is big), we need to have social support … I really believe that anyone can achieve what I did and bounce back when needed. I proved this for myself but now I need to spread it to others.

Dr. Kanter: What else do you want to do in the long term?

Dave: I dream of decreasing the impact SCD has on the wider population. Being involved in politics for instance by having run for the Geneva State Parliament or by contributing to health workgroups in political parties. Since following Geneva University’s PhD Program in global health, I have attended many health policy lectures, and I know that government has a huge role to play in putting health care policy into place that can help people get the simple care and information they need … From building more research centers, to doing research led by patients and advocacy, to improving training for caregivers, there is much more to be done!

Dr. Kanter and Dr. Issom indicated no relevant conflicts of interest.
The Promise of Novel Therapies for β-Thalassemia Syndromes

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In the past two decades, thalassemia has “graduated” from being a predominantly pediatric disease to a predominantly adult disease. While the thalassemia syndromes are heterogeneous, including homozygous or compound heterozygous β-globin defects, the pathophysiology is primarily related to ineffective erythropoiesis and systemic iron overloaded with tissue iron deposition. The major advances that have led to this dramatic improvement in life expectancy and reduction in morbidity for transfusion-dependent and non-transfusion-dependent patients include enhanced safety of the blood supply, the advent of oral chelators, the ability to noninvasively quantify tissue iron by MRI, and advances in stem cell transplantation (SCT). It is likely that even without curative treatment, children born after the year 2000 could have near normal life expectancy on regular transfusion if they chelate optimally. Additionally, in the near future, additional advances in therapy are anticipated, including optimization of gene therapy and the use of agents that leverage molecular targets.

Stringent testing of blood products has reduced the risk of transmission of viruses such as hepatitis C and HIV, which had previously wreaked havoc on this population, and now includes newer agents such as West Nile virus and severe acute encephalitis. However, parasitic infections remain a potential concern, particularly malaria, Lyme disease, and babesiosis, for which testing is less comprehensive.

The approval of not one but two oral chelators, deferasirox and deferiprone, is another key development that had a major impact on reduction in morbidity. These are agents with a longer half-life than deferoxamine, and with the convenience of oral administration, have improved compliance significantly with less iron-related cardiac and endocrine dysfunctions. The ability to combine chelators offers options for dose reduction for toxicity as well as intensification when required. Until recently, deferasirox was only available as dispersible tablets, and apart from its inconvenient mode of administration, the inactive ingredients also caused gastrointestinal intolerance. The introduction of the tablet form and granule formulation for deferasirox should improve compliance for transfusion-dependent patients. In the past two decades, thalassemia has “graduated” from being a predominantly pediatric disease to a predominantly adult disease. While the thalassemia syndromes are heterogeneous, including homozygous or compound heterozygous β-globin defects, the pathophysiology is primarily related to ineffective erythropoiesis and systemic iron overloaded with tissue iron deposition. The major advances that have led to this dramatic improvement in life expectancy and reduction in morbidity for transfusion-dependent and non-transfusion-dependent patients include enhanced safety of the blood supply, the advent of oral chelators, the ability to noninvasively quantify tissue iron by MRI, and advances in stem cell transplantation (SCT). It is likely that even without curative treatment, children born after the year 2000 could have near normal life expectancy on regular transfusion if they chelate optimally. Additionally, in the near future, additional advances in therapy are anticipated, including optimization of gene therapy and the use of agents that leverage molecular targets.

Stringent testing of blood products has reduced the risk of transmission of viruses such as hepatitis C and HIV, which had previously wreaked havoc on this population, and now includes newer agents such as West Nile virus and severe acute encephalitis. However, parasitic infections remain a potential concern, particularly malaria, Lyme disease, and babesiosis, for which testing is less comprehensive.

The approval of not one but two oral chelators, deferasirox and deferiprone, is another key development that had a major impact on reduction in morbidity. These are agents with a longer half-life than deferoxamine, and with the convenience of oral administration, have improved compliance significantly with less iron-related cardiac and endocrine dysfunctions. The ability to combine chelators offers options for dose reduction for toxicity as well as intensification when required. Until recently, deferasirox was only available as dispersible tablets, and apart from its inconvenient mode of administration, the inactive ingredients also caused gastrointestinal intolerance. The introduction of the tablet form and granule formulation for deferasirox should improve compliance for transfusion-dependent patients. In the past two decades, thalassemia has “graduated” from being a predominantly pediatric disease to a predominantly adult disease. While the thalassemia syndromes are heterogeneous, including homozygous or compound heterozygous β-globin defects, the pathophysiology is primarily related to ineffective erythropoiesis and systemic iron overloaded with tissue iron deposition. The major advances that have led to this dramatic improvement in life expectancy and reduction in morbidity for transfusion-dependent and non-transfusion-dependent patients include enhanced safety of the blood supply, the advent of oral chelators, the ability to noninvasively quantify tissue iron by MRI, and advances in stem cell transplantation (SCT). It is likely that even without curative treatment, children born after the year 2000 could have near normal life expectancy on regular transfusion if they chelate optimally. Additionally, in the near future, additional advances in therapy are anticipated, including optimization of gene therapy and the use of agents that leverage molecular targets.
ASH Officers Meet with Health and Human Services Leaders

On Thursday, July 12, ASH leadership met with two senior leaders at the U.S. Department of Health and Human Services (HHS) — the Assistant Secretary for Health, Admiral (ADM) Brett P. Giroir, MD, and the U.S. Surgeon General, Vice Admiral (VADM) Jerome M. Adams, MD, MPH, to discuss ASH’s efforts to address the burden of sickle cell disease (SCD) in the United States and globally. ASH has been making significant progress in the area of SCD since launching the SCD Call to Action in 2016, and this meeting marks the first time ASH leaders have discussed this work with the Assistant Secretary for Health and other federal public health leaders.

During the meeting, ASH President Dr. Alexis Thompson, ASH President-Elect Dr. Roy Silverstein, ASH Vice President Dr. Stephanie Lee, and ASH Treasurer Dr. Susan Shurin, identified areas where the Society and the Assistant Secretary’s office can collaborate on efforts to improve the lives of people living with SCD. Following this gathering, The Hematologist and Dr. Silverstein discussed meeting outcomes and what to expect in the future.

“The meeting revealed that the Assistant Secretary has placed SCD as one of his top priorities,” said Dr. Silverstein. “We learned that his priorities are exactly aligned with ASH’s SCD priorities and that our investments and efforts in an SCD registry, clinical trials network, guidelines, education and training, coalition, and congressional advocacy align with his goals and have his full support. This is a tremendous statement of validation for our efforts and investments and should make ASH members proud and excited to move forward.”

One major topic of potential collaboration between HHS and ASH is the Society’s newly created Sickle Cell Disease Clinical Trials Network (CTN). The goal of the CTN is to use ASH’s convening power to create a network of collaborating clinical research sites for the development and testing of interventional therapeutics and devices. Additionally, the CTN will improve accrual and reduce costs by directing trial sponsors to active SCD research sites with adequate patient populations and leverage the ASH Registry for patient cohort identification.

In addition to the CTN, the Assistant Secretary also showed support for a National Academy of Medicine study of access-to-care-related issues for people living with SCD. This type of report is ripe for collaboration with ASH as it would help federal and nongovernment entities identify gaps in SCD care and justify the need for innovative models of care for this patient population.

ASH leaders also discussed how ASH can exactly help support HHS’s national efforts on the opioid crisis. Dr. Silverstein was encouraged that Assistant Secretary Giroir shared ASH’s view that although opioids pose important public health risks, they remain an important tool for managing acute and chronic pain in patients with SCD and cancer. “His willingness to partner with ASH on getting this message out is very important,” said Dr. Silverstein, who felt that the meeting was constructive and that the positive relationships built with senior HHS leaders would yield long-term benefits. “The willingness of the Assistant Secretary to seek input from ASH on hematology-related issues and to partner with the Society to help achieve his goals represents a long-term opportunity for ASH to have a seat at the table when important decisions are made at HHS that affect hematologists and patients with blood diseases,” he said.

As a follow-up to the meeting, ASH Secretary Dr. Robert Brodsky represented the Society at a late-July HHS “Sickle Cell Disease Engagement Roundtable,” a listening session for patient organizations on SCD-related challenges and opportunities. Additionally, ASH staff has meetings scheduled with ADM Giroir’s staff to continue the discussion about specific ways to work together to help strengthen and expand federal programs focused on SCD research, training, and health care delivery. ASH will keep ADM Giroir and his office apprised as the Society advances the various components of its SCD initiative. ASH will also continue to offer the expertise of the hematology community as a resource to help advance ADM Giroir’s SCD priorities.

For more important news from Capitol Hill and advocacy-related updates visit www.hematology.org/Advocacy, and view the latest action alerts, policy news, and policy statements. You can also sign up for “Practice Update” and get this news in your inbox; make sure your subscriptions are up to date by visiting webapps.hematology.org/subscriptions.
I t is well understood that only a proportion of subjects with clonal hematopoiesis ultimately develop a hematologic malignancy. To this end, several recent studies have identified genetic alterations in hematopoietic cells in the setting of clonal hematopoiesis that confer the greatest risk of eventually developing myeloid malignancies. Despite these insights, it is still clear that for most genetic alterations commonly encountered in clonal hematopoiesis, only a proportion of subjects will develop a myeloid malignancy. For example, mutations in the epigenetic regulators TET2 and ASXL1 are found in clonal hematopoiesis, but the presence of these mutations alone cannot predict for the development of acute myeloid leukemia (AML).

Now, a thought-provoking study by Dr. Marlies Meisels and colleagues suggests that clonal hematopoiesis of the small intestine may underlie an increasing risk of developing myeloid malignancies in the setting of clonal hematopoiesis.

Prior epidemiology studies have noted a connection between chronic immune stimulation from infectious diseases or autoimmune disorders with an increased risk of developing AML and myelodysplastic syndromes (MDS). For example, in population-based registries from Sweden involving approximately 9,000 patients with AML and about 42,000 matched controls, a history of any infectious disease was associated with a significantly increased risk of AML (OR, 1.3; 95% CI, 1.2-1.4). Additionally, prior work in mice has demonstrated that systemic dissemination of bacteria induces extramedullary hematopoiesis and emergency myelopoiesis. Based on these observations, the authors used a model system for clonal hematopoiesis (mice with deletion of Tet2 in the hematopoietic system) to study the impact of microbial infection on development of myeloid malignancies from a clonal hematopoiesis state driven by Tet2 deficiency.

It is well established that like humans, only a proportion of mice with Tet2-null hematopoietic cells develop an overt myeloid malignancy, and the factors that dictate development of myeloid malignancy in Tet2 knockout (KO) mice are not well understood. The authors showed that ad libitum-fed (i.e., not germ-free) tet2 KO mice and treated with antibiotics prevented and reversed myelopoiesis in TET2 KO mice.

To unravel the molecular links between hematopoietic function and microbial infection, the authors analyzed the effects of microbial infection on IL-6 production in TET2 KO mice and controls. IL-6 is a critical activator of myelopoiesis in response to systemic bacterial dissemination and can be upregulated in myeloid malignancies. Consistent with this, IL-6 was upregulated in the plasma of TET2 KO mice and correlated with clonal expansion. IL-6 expansion was partially dependent on microbiota and could be induced by DSS or TLR2-agonist treatment. Moreover, IL-6 neutralization with an anti-IL-6 antibody could reduce myeloid disease burden in TET2 KO mice.

Overall, these data demonstrate that bacterial translocation and IL-6 production resulting from dysruption of the small intestine barrier are critical for development of myelopoiesis in TET2 null mice. Interestingly, the authors also noted that mice with Tet2 deletion in hematopoietic cells appeared to have a dysfunctional small intestine barrier and increased systemic translocation of bacteria. How mutations in hematopoietic cells in the setting of clonal hematopoiesis may impact the small intestine barrier is not clear and will likely be the subject of future work by this group. It will also be interesting to identify whether such gut dysfunction occurs in human subjects with clonal hematopoiesis. From a therapeutic perspective, these findings suggest the interesting possibility that blocking inflammatory bacterial signals in subjects with clonal hematopoiesis could reduce risk of developing leukemia. Additionally, these data suggest that targeting IL-6 may be an important therapeutic approach in patients with clonal hematopoiesis and/or overt myeloid neoplasms. It would be of interest to determine whether serum inflammatory cytokines may correlate with clone burden and risk of myeloid malignancy development in subjects with clonal hematopoiesis.

References:

Microbial Signals May Drive Leukemia Development in Subjects With Clonal Hematopoiesis


Do Plasma Levels of Direct Oral Anticoagulants Correlate With Hemorrhagic and Thrombotic Complications?


Microbial Signals May Drive Leukemia Development in Subjects With Clonal Hematopoiesis

The ability to diagnose disease accurately and to determine the most effective therapy based on key determinants of outcome in a holistic manner is the holy grail of precision medicine. For diffuse large B-cell lymphoma (DLBCL), the most common and aggressive form of non-Hodgkin lymphoma, accurate diagnosis is usually straightforward; however, our allocation of therapy remains suboptimal for the approximately 40 percent of patients not cured by standard R-CHOP (rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy alone. Better discrimination of the determinants of outcome beyond the clinically based international prognostic index (IPI) score and more effective therapies for poor-outcome subgroups are needed.

Risk stratification of patients with DLBCL has become more sophisticated in recent years. When considered in addition to the robust IPI, biological classifiers such as cell-of-origin and MYC/BCL2/BCL6 translocation status have added some value. Despite this, distinct treatment paths for biological subgroups are not routinely considered.

Furthermore, the advent and increasing use of massively parallel sequencing (MPS) has implicated somatic alteration in a large number of genes in the pathophysiology of DLBCL. Until recently, however, genomic landscape studies have been either insufficiently powered or have lacked the clinical annotation required to comprehensively define distinctive clinicopathological subgroups within the heterogeneity observed in DLBCL.

The study by Dr. Roland Schmitz and colleagues sought to explore the genomic landscape of DLBCL, and to map specific combinations of genetic changes onto cell-of-origin categories defined by gene-expression profiling. A total of 574 prospectively collected and frozen DLBCL samples underwent comprehensive, multiplatform genomic analysis (whole-exome sequencing, targeted amplicon sequencing, and RNA sequencing). The cohort was composed of the following cell-of-origin subgroups: activated B-cell-like (ABC; 51.4%), germinal-center B-cell-like (GCB; 28.6%), and unclassifiable (20.0%).

Numerous genes altered either by somatic mutation and/or copy number variation (CNV) were significantly differentially expressed across these cell-of-origin categories. This observation formed the basis of a new, validated genomic classifier consisting of four novel subgroups of DLBCL that accounted for 44.8 percent of cases in the cohort: MCD, based on MYD88 L265P and CD79B co-mutation; BN2, based on BCL2 fusion and NOTCH2 mutation; N1, based on NOTCH1 mutation; and EZB, based on EZH2 mutation and BCL2 translocation.

Three of these genomic subgroups were highly correlated with cell-of-origin gene-expression categories: MCD and N1 with the ABC category, and EZB with the GCB category. By examining the pattern of recurrent gene aberrations as well as differential gene-expression data, Dr. Schmitz and colleagues were able to identify the cellular pathways most engaged by each genomic subgroup beyond the defining features described above, including many of those unclassifiable by cell of origin.

In the MCD subgroup, dysregulation of plasmacytic differentiation, tumor suppressor gene loss, immune editing, NK-cell anergy, and an IRF4-mediated ABC gene-expression profile were prominent features. On the opposite end of the cell-of-origin spectrum, the EZB subgroup was characterized by REL amplification, tumor suppressor loss, disruption of germinal center homing, immune editing, enhanced JAK-STAT, and PI3 kinase signaling, as well as a BCL2/TCF3-mediated GCB gene-expression profile.

The other two genomic subgroups are characterized by NOTCH gene mutations and expression signatures. However, NOTCH1 mutations (which characterize the N1 subgroup) and mutations of NOTCH2 (which typify the BN2 subgroup) and the related gene SPEV were mutually exclusive, suggesting distinct pathophysiologicals. The BN2 subgroup was enriched for NOTCH and NF-κB pathway aberrations while the N1 subgroup contained aberrations affecting B-cell differentiation, which may account for the plasma-cell-like and quiescent-cell gene-expression signatures observed in this subgroup.

Clinical outcomes data were available in 240 cases of untreated DLBCL receiving R-CHOP or similar chemotherapy regimens. Approximately half of these patients could be assigned a genomic subgroup. The ability of the genomic classifier to predict for patient outcome was striking (Figure), with the BN2 and EZB subgroups enjoying significantly superior survival rates (65% and 68% 5-year overall survival [OS], respectively) when compared with the MND and N1 subgroups (26% and 36% 5-year OS, respectively).

Of note, the genomic classifier significantly improved prognostication from diagnosis when added to either the IPI or cell-of-origin classifier.

This ground-breaking work by Dr. Schmitz and colleagues has significantly enhanced our understanding of DLBCL pathophysiology and refined our ability to risk stratify patients prior to first-line chemoimmunotherapy. The validation of these results in larger cohorts is necessary, and there is clear need for ongoing work in this area, as more than half of DLBCL cases could not be genomically classified. However, a comprehensive clinicogenomic classifier that considers the IPI, cell-of-origin, and genomic subclassing concurrently is likely to provide the best possible risk stratification of DLBCL. Indeed, another recently performed landmark genomic analysis study of DLBCL by Dr. Anupama Reddy and colleagues has recently resulted in a web-based tool that attempts this very thing (dlbcl.davelab.org).

The significance of defining distinct genomic subgroups reaches well beyond the prediction of response to first-line chemoimmunotherapy. The significant risk of relapse in DLBCL, especially in patients with high IPI scores, necessitates the pursuit of nationally selected new therapies. For example, Bruton tyrosine kinase inhibitors such asibrutinib are reported to have significant efficacy in ABC-DLBCLs with both MYD88 L265P and CD79B mutations. The association of these aberrations with the MCD subgroup, together with the higher frequency of aberrations involving the B-cell receptor–dependent NF-κB pathway in the MCD and BN2 versus N1 and EZB subgroups, implies potential differential response to BTK inhibition across the genomic subgroups.

The consideration of genomic subgrouping in the design of future trials of targeted agents in DLBCL may allow for the rational selection of patients most likely to derive benefit. However, caution is warranted as not every targetable lesion will lead to disease response when hit, particularly in a complex disease such as DLBCL that can use multiple oncogenic pathways of drug escape. This was well illustrated in the aforementioned study by Dr. Reddy and colleagues, where CRISPR-based knockout of certain targetable lesions such as NOTCH2 did not have an effect on DLBCL cell proliferation in model systems.

In summary, the study by Dr. Schmitz and colleagues represents a major advancement of our biological and clinical understanding of DLBCL and represents a meaningful step toward the systematic evaluation of the role of precision medicine in this disease. However, more work is required to enable the comprehensive clinicogenomic classification of a greater proportion of cases and to lower the practical barriers to accessing sophisticated, real-time genomic testing outside highly specialized academic settings.


Recurrent Genetic
Chapuy/Shipp

MYD88, CD79B
TP53, del17p
Cluster 1
EZH2, BCL2, CREBBP

60
40
52
98

B cell–like lymphomas

Regardless of which group is correct in terms of prognosis, the identification of the same cluster of driver genes in

Dr. Chapuy and colleagues identified nearly 100 candidate cancer genes that are recurrently mutated in DLBCL, as well as

The BN2 subgroup, however, included both ABC and GCB lymphomas as opposed to the largely ABC-enriched

As expected, GCB lymphomas did poorly, with less than 40 percent of patients being alive and free of progression with

This analysis is being reported simultaneously with that of the group from the National Institutes of Health (NIH), who identified

Table. Cell-of-Origin Classifications of Diffuse Large B-cell Lymphomas

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It is difficult to know what accounts for the differences between the two analyses, specifically with respect to divergent

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The authors then demonstrated this association between JAK inhibition and an increase in the frequency of aggressive B-cell lymphomas in a mouse model. They found that Stat7 knockout in mice caused myeloid hyperplasia and B-cell transformation with subsequent development of lymphoma after bone marrow transplantation, recapitulating the clinical observation in patients. The transcription factor STAT1 is a downstream of Jak kinases. Distinct phenotypes in Jak2V617F positive MPN cases reflect differential Stat1 signaling.11

While JAK inhibitors have proven to be an effective treatment for patients with myelofibrosis, this approach provides compelling evidence that treatment may come at a cost. Increased lymphoid neoplasms represent a concern that has been raised in recent years.2,3 It is important to remember that malignancies are an ongoing risk for patients treated with JAK inhibition and an increase in the frequency of aggressive B-cell lymphomas. Notably, detection of a pre-existing B-cell clone may identify individuals at risk, potentially providing an opportunity to integrate this testing in the lymphoma risk. The authors speculate that the mechanism of disease development of lymphoma after bone marrow transplantation, recapitulating the clinical observation in patients.


1) Age of VTE

The natural history of venous thrombosis tells us that the risk of extension and/or embolization is highest within the first 30 days. Consequently, the need for therapeutic anticoagulation is critical during this time frame. After 30 days, the risk drops, which is likely why reduced or prophylactic doses of anticoagulants can be used during thrombocytopenia in this setting. While JAK inhibitors have proven to be an effective treatment for patients with myelofibrosis, this work provides an opportunity to integrate this testing in the lymphoid risk. Notably, detection of a pre-existing B-cell clone may identify individuals at risk, potentially providing an opportunity to integrate this testing in the lymphoma risk analysis when considering these therapies. The authors speculate that the mechanism of disease development of lymphoma after bone marrow transplantation, recapitulating the clinical observation in patients.

2) Location and Extent of VTE

Proximal lower-limb deep vein thrombosis (DVT) is considered more serious than calf DVT owing to the higher potential for clinically significant pulmonary embolism (PE) travelling from the larger calf veins within the lower limb. Similar PE located in the main, ilobar, or segmental pulmonary arteries is more of a concern than subsegmental PE. Anticoagulation does not lyse existing emboli, but it reduces the likelihood of recurrent PE that could prove fatal in patients who are already compromised. It is therefore reasonable to be more aggressive (see point 3) about anticoagulation for patients with a proximal leg DVT or segmental (or larger) PE, and less aggressive in patients with isolated distal leg DVT, catheter-associated upper-limb DVT, subsegmental PE, or superficial thrombophlebitis.

Severity and Expected Duration of Thrombocytopenia

A platelet count of 40 to 50 × 10^9/L is generally considered adequate for therapeutic-dose anticoagulant therapy, whereas anticoagulants should be held if the platelet count falls below 20 to 30 × 10^9/L. For patients who have an acute proximal leg DVT or segmental (or larger) PE less than 30 days old, platelet transfusion is suggested to increase the platelet count to 40 to 50 × 10^9/L to support anticoagulation. Clearly, this strategy is not feasible for patients who are refractory to platelet transfusions or patients who have prolonged thrombocytopenia (i.e., weeks to months). For patients with chronic (older than 30 days) and/or less severe VTE (see point 2) with platelet counts of 25 to 50 × 10^9/L, either half-therapeutic or prophylactic dose DVT is suggested as an alternative. Prior to implementing the anticoagulant strategies listed here, heparin-induced thrombocytopenia as an alternative diagnosis must be considered and additional risk factors for bleeding should be reviewed (e.g., coagulopathy, renal, or liver dysfunction).

Finding direct evidence to support 50 × 10^9/L as a safe threshold for surgery is also surprisingly difficult. Most platelet transfusion guidelines reference expert opinion as the reason for selecting that particular threshold.11 The highest quality of evidence comes from a recent retrospective review of 95 patients with acute leukemia who underwent 167 operations prior to 1988. All patients were given platelet transfusions to raise their counts to 50 × 10^9/L. The procedures ranged from major operations (e.g., laparotomy, craniotomy) to minor procedures (e.g., catheter insertion, tooth extraction). Reassuring, only 7 percent of patients experienced more than 500 mL of blood loss, and there were no deaths due to surgery-related hemorrhage. Extrapolating from these results, it is reasonable to conclude that the risk of bleeding should be low in anticoagulated patients who have a platelet count of at least 50 × 10^9/L.10

In summary, within the limitations of this “no data zone,” the guidelines for management of cancer-associated thrombosis during thrombocytopenia outlined by ISTH provide clinicians with a fence to walk on between bleeding and recurrent thrombosis.

Circulating Tumor DNA in Lymphoma Monitoring

Mutations can be found in key pathways with a predominance of STAT6 hotspot variants in cHL. STAT6 was the most commonly mutated gene (37.5% of cases) in this study. In the chemotoxic therapy group, Dr. Tiacci and colleagues found that the JAK-STAT pathway was implicated in over 87% of cHL cases. Other recurrent pathways included the NF-kB (46.2% of cases), PI3K/AKT (46.2%), epigenetic (35.0%), immune surveillance (27.5%), and NOTCH (20.0%) pathways. This pathway distribution is different from DLBCL but similar to that seen in primary mediastinal B-cell lymphoma.

In summary, this study showcases the utility of ctDNA monitoring in cHL. This methodology highly correlates with the percentage of mutations in genes such as ARID1A, TE2, BCCR, SPEN, EP300, KMT2D, and XPO1 (Figure 1A). By contrast, those patients who received immunotherapy effectively cleared their founder clones with emergence of new clonal events (Figure 1B).

ctDNA predicts response to therapy in cHL. Similar to prior studies in DLBCL, the researchers suggest an optimized cut-off of a two-log reduction in ctDNA load in response to chemo-agent therapy to predict complete response and cure (p < 0.001) (Figures 1C and 1D). By contrast, PET/CT in cHL is plagued by the fact that glucose uptake largely measures the inflammatory component of cHL and not the tumor burden. These results suggest that ctDNA may complement (or even ultimately replace) PET/CT monitoring.

The investigators then generated a genetic knockout of a transcription factor (mitfa) that controls melanocyte differentiation and created zebrafish that lacked melanocytes. Importantly, this did not entirely disrupt the stem cell niche such that normal numbers of stem cells and blood cells were still seen under resting laboratory light conditions. However, the team then went on to apply the challenge of ultraviolet light (UVB: 280-315 nm), giving a dose equivalent to that which would create sunburn in a fair-skinned person. The zebrafish larvae tolerated UVB well, but in the melanocyte-deficient animals there was an increase in UV-induced DNA damage and a decrease in both HSPC number and blood cell production. As further evidence for the protective effect of the melanocyte cover, similar findings were observed when melanin production was inactivated. A further experimental innovation was to anaesthetize the larvae such that they rolled upside down on their backs and the HSPCs were directly exposed to UVB challenge. In this situation, the damaging effects of UVB were seen even in the wild type animals, indicating that the anatomical orientation of the melanocytes is critical.

Comparative studies in many other fish also revealed melanocytes covering the hematopoietic kidney marrow. In contrast, the HSPCs in all animals found on land are exposed to intense sunlight in their natural habitat. The investigators suggest that melanocytes are exposed to intense sunlight in their natural habitat. The investigators suggest that melanocytes can provide protection from ionizing radiation that could damage the DNA of these critical stem cells. However, ionizing radiation, which can strip electrons from atoms and includes gamma rays and X-rays, is mostly filtered out by sunlight, and so the team wondered if the melanocytes might act to protect aquatic HSPCs from nonionizing radiation such as ultraviolet light. Indeed, zebrafish mostly swim in shallow water around paddy fields, and as such, are exposed to intense sunlight in their natural habitat.

Like many of us, when I sit down with a patient to review their diagnosis, I start with a cartoon drawing of a bone. Often, as I have sketched out the function of stem cells and given a short description in hematopoiesis and blood-cell pathology, it’s occurred to me how much we don’t know about this process.

A recent, fascinating article by Dr. Friedrich Kapp and colleagues points to the resolution of a question that has troubled me for many years: why do bone marrow have to be located in the middle of bones?

Hematopoietic stem cells are always on the move. During human development, they migrate from the aorta-gonad-mesonephros region to the fetal liver and then to the bone marrow around the time of birth. Over the course of evolution, they moved from the kidney marrow to fish into the bone marrow in fish. So what are the selective forces that drove this path?

This is the question that lies at the heart of this recent article published in Nature. The authors noted that the hematopoietic stem and progenitor cells (HSPC) in the kidney marrow of zebras were covered by a mantle of melanocytes. The authors were aware that in 1979 Dr. Edwin Cooper suggested that HSPCs were located in the bone marrow of land animals as this provided protection from ionizing radiation that could damage the DNA of these critical stem cells. However, ionizing radiation, which can strip electrons from atoms and includes gamma rays and X-rays, is mostly filtered out by sunlight, and so the team wondered if the melanocytes might act to protect aquatic HSPCs from nonionizing radiation such as ultraviolet light. Indeed, zebrafish mostly swim in shallow water around paddy fields, and as such, are exposed to intense sunlight in their natural habitat.

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Comparative studies in many other fish also revealed melanocytes covering the hematopoietic kidney marrow. In contrast, the HSPCs in all animals found on land are located within the bone marrow. The final beautiful coda in the report was the demonstration that tadpoles of frogs have melanocytes around HSPCs in the kidney marrow, but that the HSPCs move to the bone marrow at the time that the limbs develop. The presence of the cortical bone was indeed then shown to provide strong protection against UVB-induced damage.
Redefining Risks in Multiple Myeloma is Still a Work in Progress


Multiple myeloma (MM), a terminally differentiated plasma cell malignancy, is one of the most clinically and genetically heterogeneous cancers. Even in the era of novel therapeutic agents, risk-stratification for myeloma survival, MM treatment outcomes, response to therapy, and myeloma remains an incurable disease. In that regard, much effort has been put into understanding the pathogenesis and predicting which oncogenic mutations or genes contribute to disease. As such, the International Myeloma Working Group (IMWG) has stratified MM patients into three distinct risk classifications: standard risk (hyperdiploidy, [11;14], [16;14]), intermediate risk ([14;16], del[13q]), and high risk ([11q), [14;16], [14;20]). Nonetheless, there is an ongoing effort to further risk-stratification, which is crucial for clinical decision-making.

With the huge advancement in genomic technologies during the past decade, more specific molecular classifications were discovered and proposed for risk-stratification. Although genetic expression profiles (GEP) on microarrays were heavily studied and yielded high-risk signatures that were incorporated into the University of Arkansas for Medical Sciences (UAMS) and the Intergroup Francophone du Myelome multicenter risk without any a prognostic tool. Currently, no data set remains to be the gold standard for risk-stratification. While clinical lab values have been associated with prognosis and treatment outcomes, the oncogenic landscape of myeloma seemed to be a prominent determinant of prognosis. As such, the International Myeloma Working Group (IMWG) has stratified MM patients into three distinct risk classifications: standard risk (hyperdiploidy, [11;14], [16;14]), intermediate risk ([14;16], del[13q]), and high risk ([11q), [14;16], [14;20]). Nonetheless, there is an ongoing effort to further risk-stratification, which is crucial for clinical decision-making.

However, given the genomic complexity of myeloma, we believe that more alterations will be discovered at the epigenetic level as well as in the intronic regions, with ongoing whole-genome sequencing being done on tumor samples of large cohorts, which could in turn be used as prognostic biomarkers.

Around two years ago, the Myeloma Genome Project (MGfP) was announced at the 58th ASH Annual Meeting. The project aims to integrate high-quality genomic data of newly diagnosed treatment-naїve MM patients, collected by UAMS Myeloma Institute, the Myeloma Xi trial (United Kingdom), the Intergroup Francophone du Myelome multicenter risk without any a prognostic tool. Currently, no data set remains to be the gold standard for risk-stratification. While clinical lab values have been associated with prognosis and treatment outcomes, the oncogenic landscape of myeloma seemed to be a prominent determinant of prognosis. As such, the International Myeloma Working Group (IMWG) has stratified MM patients into three distinct risk classifications: standard risk (hyperdiploidy, [11;14], [16;14]), intermediate risk ([14;16], del[13q]), and high risk ([11q), [14;16], [14;20]). Nonetheless, there is an ongoing effort to further risk-stratification, which is crucial for clinical decision-making.

The ironic and seemingly paradoxical finding is that patients were classified as high-risk by IMWG criteria and low-risk by recursive multivariate model. Though this could truly mean that there is no significant effect of these mutations to just a gain of CKS1B, which was found in 21.9 percent of patients. While other mutations were analysis of a 17p loss. Conversely, an amplification of more than four copies of CKS1B, which constituted genetic alterations on progression, relapse, and treatment resistance.

In this article, Dr. Walker and colleagues implemented a recursive partitioning model on existing screening data to discover that a worse prognosis could be predicted in MM patients in the presence of a bi-allelic inactivation of TP53 or the amplification of 4 copies of CKS1B (1q21) in the context of ISS III staging. This subset of patients, the double-hit group, has a significantly diminished median progression-free survival (PFS) of 15.4 months and median overall survival (OS) of 20.7 months compared with the low- and intermediate-risk patients. Their model defined “low-risk” as patients having low or intermediate disease stage without any genetic factors, while the intermediate-risk was defined by either ISS I plus 4 (14;14) or del(17p), or ISS III with no genetic factors. Interestingly, the bi-allelic inactivation of TP53 turned out to be a prominent determinant of PFS and OS prognosis; upon review, del(17p) is no longer prognostically valuable for identifying the higher importance of this sequence analysis of a 17p loss. Conversely, an amplification of more than four copies of CKS1B, which constituted a small fraction of 6.3 percent of patients, was associated with an even worse PFS and OS compared to low-risk patients. CKS1B, which was found in 21.8 percent of patients. While other mutations were found to be significantly associated with poorer outcomes at a univariate level, they were excluded in the multivariate model.

The importance of including the mentioned genetic factors mentioned here into a future risk-stratification model is illustrated by the fact that patients in the double-hit group performed poorly, irrespective of IMWG risk stratification, while patients classified as high-risk by IMWG criteria and low-risk by recursive partitioning had OS and PFS similar to that of those classified as low-risk by IMWG criteria and intermediate-risk by recursive partitioning. This raises a longstanding concern: not having a concrete risk-stratification model that clearly guides clinical management in MM. However, we are on the right path to achieving that goal. Most notably, the MMRF’s Clinical Outcomes in MM (COnC) study is a significant initiative to collect clinical and genomic data on more than 1,200 patients with newly diagnosed MM over a longer follow-up and sequence tumor samples to monitor genomic alterations with time.

To date, researchers have collected genomic data on more than 1,200 patients, including whole-exome, whole-genome, and targeted DNA sequencing data. Massive Real-Time Sequencing of tumor samples with a small biobbles that we believe to map out the genomic landscape of this complex disease to predict survival and treatment response, and devise targeted therapies accordingly. Indeed, because of the current genomic studies of myeloma, several clinical trials aim at targeting defective genes and pathways have already been conducted or are still ongoing (i.e., RAS/RAF/MEK, FAK/Akt, Cyclin D, and the BCL2 pathway). Just imagine what would happen if we further improve the significance of these interactions and identify additional epigenetic mechanisms in thousands of newly diagnosed, relapsed, and treatment-refractory myeloma patients. The newly identified double-hit group would be just the beginning of many risk-stratifiers to come.

Putting in the (Net)Work to Cure SCD

As part of its broader effort to identify new treatment strategies and secure a pathway to curing sickle cell disease (SCD), globally, ASH is in the process of establishing a clinical trials network (CTN) to identify high-priority research questions and support efforts to address these questions. In July 2018, ASH brought on Dr. Charles Cheson to serve as medical staff as director of the clinical trials programs, and services to help overcome the challenges of conducting clinical trials in SCD, including a comprehensive patient engagement strategy to increase understanding of both the disease and clinical trials overall.

In this Q&A, Dr. Cheson explains more about his role and the direction of the network in the near future.

Q: What is your message for members who would like to get involved and help spur progress in the arena?

A: As we start to build this network, we want to hear from the SCD stakeholders, especially those who have been involved in SCD clinical trial activities and who would like to volunteer their expertise to assist with ongoing efforts. If you are interested in learning more about volunteer opportunities or how to become an official site for the CTN, please contact us at SCDCNTN@hematologist.org.
A New Strategy for the Prevention of Adverse Maternal and Fetal Outcomes in Pregnant Women with Sickle Cell Disease: The Oxygen Therapy and Pregnancy in SCD Trial (DR02G)


**CLINICALTRIALS.GOV IDENTIFIER:** NCT02813850

**PARTICIPATING CENTERS:** Hôpital Necker-Enfants-Malades (Public Hospitals of Paris) and nine French hospitals

**ACCRUAL GOAL:** 200 participants

**STUDY DESIGN:** This is an open-label, randomized, multicenter trial. Participants, pregnant women with sickle cell disease (SCD), are randomly assigned to home-based oxygen therapy or no home-based oxygen therapy. Primary and secondary measures will include occurrence of at least one vaso-occlusive complication lasting more than 24 hours during pregnancy and 30 days postpartum, respectively.

The biological premise for both the obstetric and cognitive trials is that improvement in nocturnal oxygen saturation will have significant increase in oxygen delivery and will improve the clinical outcomes of interest. An alternative strategy, and perhaps complementary strategy to improve oxygen delivery to vital organs, includes therapeutic agents that will increase baseline hemoglobin levels such as regular blood transfusion, hydroxyurea, or other investigative agents. Conceivably these therapeutic agents would have a more sustained impact than nocturnal oxygen supplementation or overnight autoadjusting continuous airway pressure. However, these have not been tested in pregnancy because pregnant women typically are excluded from therapeutic trials that are intended to increase baseline hemoglobin levels.

Unfortunately, the results of DR02G will not be transferable to at least 90 percent of the pregnant women with SCD living in lower middle-resource settings. Alternative strategies will need to be considered for this population. Regardless of the results of DR02G, the SCD community will anxiously await completion of the trial as it will provide important prospectively and rigorously obtained estimates for adverse obstetric and perinatal related outcome measures for women with SCD living in higher resource settings. The investigative team is to be congratulated for addressing an emerging clinical challenge for young women with SCD wanting to start their family.}

**COMMENT:** Oxygen trials in SCD are not new. One randomized controlled trial compared overnight autoadjusting continuous airway pressure plus standard care versus standard care alone for six months, resulting in improved cognitive morbidity. The phase II trial in children and adults with SCD was based on an early safety trial showing no adverse events associated with the administration of oxygen for six weeks in children with SCD. The primary outcome is the cancellation subset from the Wechsler scales. Secondary outcomes include, but are not limited to, general cognitive function, quantitative brain MRI, quality of life, and daily pain via a smartphone App (GoMedSolutions, Inc.).

**Figure 1. Forest Plot Showing the Effect of Sickle Cell Disease (SCD) on Maternal Mortality in Pregnant Women With and Without SCD.**

**Figure 2. Forest Plot Comparing the Effect of Sickle Cell Disease (SCD) on Perinatal Mortality Among Women With and Without SCD.**


Other secondary outcome measures include, but are not limited to, pregnancy-induced hypertension, pre-eclampsia, eclampsia, and perinatal and neonatal death rates. A vaso-occlusive event is defined as pain in the bones, acute chest syndrome, ischemic stroke, cardiomyopathy, pulmonary hypertension, splenic and hepatic sequestration, and death of the mother. A total of 200 women are expected to be enrolled throughout a course of six years, with expected trial completion in February 2021.

**RATIONAL:** As survival for women with SCD continues to improve in both high- and low-resource settings, researchers expect that more women with SCD will become pregnant and thus susceptible to adverse obstetric events and SCD-related complications during pregnancy. Maternal and newborn complications are well recognized in pregnant women with SCD. A pooled analysis of pregnant women with SCD indicated that maternal and perinatal mortality odds ratios (ORs) were significantly higher compared with those of women without SCD (OR, 10.91 [95% CI, 1.83-65.11] vs. 3.76 [95% CI, 2.34-6.66], respectively); Figures 1 and 2. Pregnant women with SCD have higher rates of adverse maternal and fetal complications, including not being pre-eclampsia and intrauterine growth restriction (pooled OR, 2.05 [95% CI, 1.47-2.85] vs. 1.29 [95% CI, 1.85-4.21], respectively). Few randomized controlled trials on preventing these adverse events in pregnant women have been conducted, and no evidence-based strategy has emerged as an effective intervention to prevent these life-threatening and life-alternating complications of pregnancy in women with SCD.

**ANTIBODY THERAPY IN ACUTE MYELOID LEUKEMIA CONDITIONING: CAN WE IMPROVE UPON THE DEPTH OF RESPONSE?**

**STUDY TITLE:** Study of Iomab-B Prior to HCT vs. Conventional Care in Older Subjects With Active, Relapsed or Refractory AML (SIERRA)

**ISRCTN NUMBER:** NCT02656065

**SPONSOR:** Actinium Pharmaceuticals

**ACCRUAL GOAL:** 150 patients

**PARTICIPATING CENTERS:** 16 centers around the United States

**STUDY DESIGN:** This is a phase III randomized study of adding Iomab-B, a monoclonal antibody directed against CD45 and linked to radioisotope iodine-131, to a reduced-intensity conditioning (RIC) regimen and protocol-specified allogeneic hematopoietic stem cell transplantation (HSCT) for patients with relapsed or refractory acute myeloid leukemia (AML) older than 55 years.

**PRIMARY ENDPOINT:** Durable Complete Remission (dCR) defined as CR or CRp lasting at least 180 days.

**SECONDARY ENDPOINTS:** Overall Survival (OS) at one year from randomization

**RATIONAL:** Relapsed or refractory AML is a devastating condition. Once CR is achieved, approximately 50 percent of patients younger than 60 years, and up to 90 percent of patients older than 60 years will relapse despite consolidation strategies. Primary refractory disease is present in between 20 to 25 percent of patients. Allogeneic stem cell transplantation (ASCT) offers the best hope of durable remission or cure, yet many older patients have health conditions that prevent the use of myeloablative strategies (which result in total body radiation) during conditioning. This puts them at high risk for post-transplant rejection.

Strategies that have tried to increase the intensity of preparative regimens may increase non-relapse mortality. This study incorporates targeted marrow ablation with a CD45 monoclonal antibody conjugated to the radiisotope iodine-131 as part of a reduced-intensity conditioning regimen. The aim is to test the hypothesis that a radioimmunoconjugate provides improved pretransplantation disease control and prolongs the remission duration in this very high-risk population.

**COMMENT:** There is no true standard of care for relapsed/ refractory AML. For patients with fitness to proceed to ASCT, salvage chemotherapy is aimed at inducing a remission, or at least disease reduction, as a bridge to transplantation. Salvage regimens vary, and few have been rigorously compared against one another to establish relative efficacy or toxicity. Most include high-dose cytarabine, purine analogs, or anthracyclines. And yet, we know that disease control prior to transplantation is a key factor in that undertaking’s success. Either failure to achieve a remission or the presence of minimal residual disease prior to allogeneic hematopoietic cell transplantation have been associated with worse outcomes.
with increased risk of relapse and death in patients with AML.\(^1\)\(^2\)\(^3\) It is unclear whether even myeloablative conditioning can overcome inadequate disease control.\(^4\) And what about patients with comorbidities? Reduced-intensity transplantation, which lacks at least a portion of its success on graft-versus-tumor effect, may be especially handicapped by residual disease.

Thus, this is an area ripe for clinical research. There have been several approaches. One is a bridging strategy where patients are taken directly to transplantation if they achieve at least some cytoreduction with salvage therapy — typically roughly two weeks after attempt at remission.\(^4\) A second approach is the use of mutation-directed agents such as incorporating therapy targeted against the Fms-like tyrosine kinase 3 internal tandem duplication, or aberrant isocitrate dehydrogenase. Incorporating antibodies into salvage or conditioning is also an option.

In 2009, researchers at the Fred Hutchinson Cancer Center published results of 58 patients older than 50 years who were treated with this iodine-131-labeled anti-CD5 antibody.\(^1\) The agent was designed to deliver targeted hematopoietic irradiation to the marrow, spleen, and lymph nodes prior to transplantation and was combined with a standard reduced-intensity conditioning regimen. The combination produced complete remission in all patients without impairment of engraftment. Twelve percent of patients died of nonrelapse causes by day 100, and the rate of recurrent disease was 40 percent at one year. A similar study of 16 patients younger than 50 years was published in 2014.\(^5\) Both were aimed at finding a maximal-tolerated dose of the \(^{131}\)I-ICB-Ab, now called "loom-B.

The current study aims to test this preliminary data in a large number of patients at multiple centers. Researchers are recruiting patients older than 55 years with active, relapsed, or refractory AML. Patients will then be randomized to salvage therapy or to the loom-B treatment group. In the investigatory arm, patients will get an individualized dose of the radioimmunoconjugate and then proceed to a fludarabine and low-dose TBI conditioning regimen following by infusion of donor cells. Patients on the control arm will get salvage therapy. They may cross over to the radioimmunoconjugate arm if not in CR.

Whether this strategy works and produces durable remissions remains to be seen. However, it does emphasize a true need in this patient population. While improvements in supportive care and graft-versus-host disease treatments are essential, relapse is the greatest threat to survival after an allograft for high-risk AML. Deeper pretransplantation remissions achieved safely must remain a key investigatory priority.

1. Wattad M, Weber D, Döhner K, et al. Impact of salvage regiments high-risk AML. Deeper pretransplantation remissions achieved in this patient population. While improvements in supportive care and graft-versus-host disease remains to be seen. However, it does emphasize a true need in this patient population. While improvements in supportive care and graft-versus-host disease treatments are essential, relapse is the greatest threat to survival after an allograft for high-risk AML. Deeper pretransplantation remissions achieved safely must remain a key investigatory priority.

2. whether even myeloablative conditioning can overcome inadequate disease control.\(^4\) And what about patients with comorbidities? Reduced-intensity transplantation, which lacks at least a portion of its success on graft-versus-tumor effect, may be especially handicapped by residual disease.

3. Whether this strategy works and produces durable remissions remains to be seen. However, it does emphasize a true need in this patient population. While improvements in supportive care and graft-versus-host disease treatments are essential, relapse is the greatest threat to survival after an allograft for high-risk AML. Deeper pretransplantation remissions achieved safely must remain a key investigatory priority.

4. 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.

The Hematologist
A Transplant Patient With Visual Disturbance

LYNDSEY RUNAAS, MD,* AND STEVEN KROFT, MD†
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A 34-year-old woman presented to clinic on day 95 following allogeneic, myeloablative matched unrelated bone marrow transplantation with cyclophosphamide and total body irradiation conditioning for T-cell acute lymphoblastic leukemia. Transplantation had been complicated by pericardial effusion secondary to tacrolimus and by grade 1 graft-versus-host disease of the skin, both of which had resolved. She remained on sirolimus and prednisone 10 mg daily for immune suppression; she then developed sudden onset visual changes. A comprehensive eye examination noted no intraorbital pathology but demonstrated postchiasmal incongruous left hemianopsia. A brain MRI scan revealed a peripherally enhancing lesion centered in the right thalamus and subcentimeter enhancing lesions associated with petechial hemorrhage at the surface of the right superior colliculus and cerebellar vermis (Figure 1). Lumbar puncture was performed, but cerebrospinal fluid (CSF) analysis did not provide a diagnosis. The patient then underwent a brain biopsy with results below (Figures 2-4).

What is the diagnosis?
A. Central nervous system relapse of T-precursor acute lymphoblastic leukemia
B. Post-transplant lymphoproliferative disorder
C. Toxoplasmosis
D. Cryptococcus

Figure 1. Representative brain imaging
Figure 2. Low-power pathologic image showing fragments of brain tissue with areas of necrosis (arrowheads), as well as a patchy lymphoid infiltrate, including distinctly perivascular infiltrates (arrow).
Figure 3. High-power image magnifying arrowed sections in Figure 2.
Figure 4. High-power image magnifying round structure seen to the left of the blood vessel in Figure 2.

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

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

Remembering Dr. Michael C. Lill (1959-2018)

Dr. Michael C. Lill passed away Tuesday, June 19, 2018. He served on the ASH Committee on Government Affairs and participated in the 2014 ASH Advocacy Leadership Institute, as part of his efforts to advocate for hematology research funding and push the field forward to conquer blood diseases worldwide. Learn more about his contributions to hematology in a tribute now available in the Society Pages in ASH Clinical News. Read the In Memoriam online at www.ashclinicalnews.org.