Although monitoring of select protein biomarkers has long been an integral part of standard oncology care (e.g., prostate specific antigen), methods with sufficient analytical sensitivity to enable detection of 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 [PET] and computed tomography [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 gene rearrangements in diffuse large B-cell lymphoma 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 gene rearrangements in diffuse large B-cell lymphoma). Subsequent studies introduced the use of somatic tumor variants for this purpose.2,3 Now, Drs. Valeria Spina and Alessio Bruscaggin 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 cells in a predominant inflammatory background is even more astounding. Drs. Spina and Bruscaggin’s study makes several key points, as outlined in the following sections:

- **ctDNA identifies tumor-specific variants in cHL.** Mutations in the ctDNA were compared to paired tumor gDNA, with 87.5 percent detectable in cDNA of variants identified in the tumor. None of those variants were detected in paired tumor background tissue without neoplastic cells, confirming their origin in the neoplastic cells. Additively, all germline variants were excluded through comparison with paired normal gDNA from granulocytes. Additively, all germline variants were excluded through comparison with paired normal gDNA from granulocytes. Overall, somatic mutations were identified in 81.2 percent of cHL cases, with a mean of five mutations per case.

- **ctDNA 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 a 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 (p < 0.01). Summing the ctDNA burden, there was a 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.

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a historically rare, highly aggressive disease for which there are no approved or standard therapies, and median overall survival (OS) reported by most groups is eight to 14 months, despite use of multagent cytotoxic chemotherapy programs as used in acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), or lymphomas.1-4 Originally classified as a member of the AML-related family of neoplasms by the World Health Organization (WHO) in 2008,5 greater understanding of BPDCN’s unique clinical presentation, clinical course, and disease biology has justified classification into its own category under myeloid neoplasms in the WHO 2016 reclassification.6 Clinically, BPDCN affects the skin most commonly, followed by the bone marrow or lymph nodes, with other extramedullary sites also commonly involved. While there is no dominant, recurring cytogentic lesion defining BPDCN, the most commonly occurring molecular mutations include TET2, ASXL1, RAS, and TP53; not only are these mutations consistent with mutations occurring in the myeloid malignancies, but we and others also have observed that myelodysplastic syndromes (MDS)/chronic myelomonocytic leukemia (CMML) frequently co-occur with BPDCN.6-8 In terms of diagnostics, there is now a defined immunophenotypic triad that helps to identify the disease: CD4+CD56+CD123+ (pneumonic: think “CD123456”) with other markers such as TCL-1, Cxcl3, and TCF4 further adding specificity to the diagnosis and helping the clinicopathologic team to distinguish among other competing/mimicking diagnoses.6,7,9 The major conceptual breakthrough in the field has been the recognition of overexpression of IL3R (CD123) at the level of the leukemia stem cell in most patients with AML and in virtually 100 percent of patients with BPDCN.6,10 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.10,11 Therefore, new therapeutic approaches based on these scientific breakthroughs are sorely needed.12

**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. An initial 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 was given a working diagnosis of a nonspecific skin infection, was prescribed antibiotics, and was asked to return. Upon return three weeks later, the skin lesions had not resolved, with several more appearing in the trunk and lower extremities. The clinic performed a biopsy of one of the target lesions, with the differential diagnosis in this previously healthy patient including various common skin infections and occasional non-Hodgkin lymphoma. To the surprise of the local team and the patient, the final diagnosis was BPDCN. With an ECOG performance status of zero, the patient inquired about frontline therapy options and was referred to our clinic for discussion of clinical trial approaches.

**Patient Management**

With its history of confusing nomenclature and diverse clinical manifestations, BPDCN has been a truly problematic 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, but this is still associated with a poor prognosis and rapid evolution to an acute leukemia state in many patients, despite no marrow involvement at baseline.6 We stage all patients with BPDCN to reflect the three most common compartments of involvement — skin, bone marrow, lymph nodes. In fact, this patient had involvement of all three; bone marrow was ultimately positive for involvement (with flow and IHC demonstrating CD4+CD56+CD123+), and computed tomography imaging revealed lymph node enlargement.

Groups worldwide have borrowed from the experience of acute leukemia and lymphoma for delivery of therapeutic regimens to patients with BPDCN.6-10 In our own experience with the ALL-based regimen (F6C ADV alternating with methotrexate and Ara-C), we observed a greater than 80 percent overall response rate (ORR) in the frontline setting; however, relapses occur at a high rate, and the median OS still remains at two years or less, and the most common causes of death remain relapse and multiorgan failure. On the basis of the finding of almost universal positivity for CD123, we performed a small pilot study for patients with BPDCN with a CD123-targeting agent known as diphtheria toxin-interleukin-3 (DT-IL-3), later known as SGN-35 (tagraxofusp, Stemline Inc). In this study, seven of nine evaluable
President’s Column

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 network 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 identifies 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

NIH Announces Cure Sickle Cell Initiative

The National Institutes of Health announced this month the launch of the Cure Sickle Cell Initiative, a collaborative research effort to accelerate the study of curative gene therapies for sickle cell disease (SCD). The initiative will take advantage of the latest genetic discoveries and technological advances to move the most promising genetic-based curative therapies safely into clinical trials.

In a recent statement, ASH President Dr. Alexis Thompson states: “SCD is a chronic and debilitating genetic blood disease for which there are few treatments and curative options ... The Cure Sickle Cell Initiative is a bold and visionary plan to bring potential cures to the broader community of individuals living with SCD. The fact that the National Institutes of Health has taken on this important challenge sends a powerful message to individuals with SCD and their health care providers that moving promising science from the laboratory bench to the clinic is a real priority for the United States government.”
2018 Honorific 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 contribution to hematology.

**WHO:** Victor Hoffman, DM, FRCP, FMedSci, University College London
**WHAT:** Wallace H. Coulter Award for Lifetime Achievement in Hematology
**WHEN:** Sunday, December 2, 2018, at 1:30 p.m.
**WHERE:** Hall A/B, San Diego Convention Center

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

**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.”

**WHO:** Ross L. Levine, MD, Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College
**WHAT:** William Damashek Prize
**WHEN:** Tuesday, December 4, 2018, at 9:30 a.m.
**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 myeloproliferative neoplasms. He is among the several investigators who have driven the paradigm shift of leukemia research from simple allelic-loss to gene expression to the development of novel therapeutic strategies.

**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.”

**WHO:** Alan D. D'Andrea, MD, Harvard Medical School and Dana-Farber Cancer Institute
**WHAT:** Ernest Beutler Lecture and Prize
**WHEN:** Monday, December 3, 2018, at 1:30 p.m.
**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.

**WISDOM:** “More than any other disease subspecialty, hematology has provided an ideal environment for those interested in clinical and translational science. The interchange between scientists’ and clinicians’ work. Then enjoy the revels!”

**WHO:** Neil S. Young, MD, Nat’l Institutes of Health
**WHAT:** Ernest Beutler Lecture and Prize
**WHEN:** Monday, December 3, 2018, at 1:30 p.m.
**WHERE:** Hall A/B, San Diego Convention Center

**WHY:** Dr. Young is being recognized for his work 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.

**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 you of thinking and looking at the world, not the way everyone else does them. And be persistent.”

**WHO:** Brunoangel Falini, MD, University of Perugia and the Institute of Hematology and Bone Marrow Transplantation in Italy
**WHAT:** Henry M. Stratton Medal
**WHEN:** Tuesday, December 4, 2018, at 9:30 a.m.
**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.

**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 pass-=n, determinate-=n, and innovate-=n play a very important role.”

**WHO:** Frieda K. Stevenson, DPh, University of Southampton and Southampton University Hospitals, UK
**WHAT:** Henry M. Stratton Medal
**WHEN:** Tuesday, December 4, 2018, at 9:30 a.m.
**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.

**WISDOM:** “Hematology should be the best discipline to translate laboratory findings to the clinic. So, work in an institute where this is encouraged. B-logy and the clinic have always been closely aligned in hematology; so check that the interchange between scientists’ and clinicians’ work. Then enjoy the revels.”

**WHO:** Connie J. Eaves, PhD, FRS (Canada), Corresponding FRS (Edinburgh), BC Cancer Agency and University of British Columbia
**WHAT:** E. Donnall Thomas Lecture and Prize
**WHEN:** Monday, December 3, 2018, at 9:00 a.m.
**WHERE:** Hall A/B, San Diego Convention Center

**WHY:** Dr. Eaves is recognized for her outstanding contributions to the field of hematopoiesis and stem cell research, as well as her work mentoring other leaders in the field.

**WISDOM:** “Seek strong mentors whose knowledge and science inspires and motivates you to be so far challenged. Develop an honest and ongoing knowledge of what you need and want in a career trajectory where you will have to continuously make choices. Anticipate change and learn how to program and manipulate large datasets.”

**WHO:** Jose A. Lopez, MD, University of Washington
**WHAT:** ASH Award for Leadership in Promoting Diversity
**WHEN:** Sunday, December 2, 2018, at 1:30 p.m.
**WHERE:** Hall A/B, San Diego Convention Center

**WHY:** Dr. Lopez 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.

**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 you of thinking and looking at the world, not the way everyone else does them. And be persistent.”

**WHO:** Cage S. Johnson, MD, University of Southern California
**WHAT:** ASH Award for Leadership in Promoting Diversity
**WHEN:** Sunday, December 2, 2018, at 1:30 p.m.
**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.

**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)
Ask the Hematologists

(Cont. from page 1)

patients achieved a major response with one cycle of available drug, free of which were CIs.12 On this basis, we set the study to continue on new patients in multiple cycles of SL-401.13 As updated recently at the 2018 European Hematology Association Annual Congress, 45 patients treated across all clinical trials with SL-401 as a single agent at 12 ng/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 has been found to be expected and generally manageable with safe parameters in these; there does be assessment of baseline heart and organ function and careful daily assessments of clinical parameters prior to each dose, including albumin levels, weight, renal function, and liver function. Now, with median follow-up of 13.8 months (range 0.2-37.4 months), the median OS has not yet been reached among frontline treated patients at 12 ng/kg/day dosing.21

Patient Disposition and Long-Term Follow-Up

Historically, we have treated younger patients with ALL- based chemotherapy such as hyper-CVAD. We reviewed cytogenetic changes versus clinical trial options. After discussion about the natural history of BPDCN and limited therapy options, the patient opted for additional treatment with SL-401. He received a total of five cycles, achieved a CR, maintained it 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 progress to an alloeneic SCT in CR1. Post-SCT, he was monitored closely and experienced go well until 1 year before his death in 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 progression-free survival, the patient’s condition was well maintained. When available, the SL-401 clinical trial has now become our de facto frontline standard of care for patients with BPDCN.

Future Directions and Therapy Strategies

In terms of targeting CD123, an emerging area of research is yielding novel therapeutic approaches with monoclonal antibodies, bispecific antibodies, immunotherapy, and CAR-T therapies.17 Moving beyond single-agent CD123, therapeutic options for clinical trial with frontline SL-401. He received a total of 5 cycles, achieved a CR, maintained it 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 progress to an alloeneic SCT in CR1. Post-SCT, he was monitored closely and experienced go well until 1 year before his death in 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 progression-free survival, the patient’s condition was well maintained. When available, the SL-401 clinical trial has now become our de facto frontline standard of care for patients with BPDCN.

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Attendance at the 2018 ASH Annual Meeting

Alison Loren, chair of ASH’s Committee on Training, admits that she was craving innovation as she met with colleagues to discuss Trainee Day, held each year at the ASH Annual Meeting. “We’ve learned, as was the occurrence of capillary leak syndrome (CLS), which constituted 20 percent of all adverse events at all grades. CLS has been found to be expected and generally manageable with safe parameters in these; there does be assessment of baseline heart and organ function and careful daily assessments of clinical parameters prior to each dose, including albumin levels, weight, renal function, and liver function. Now, with median follow-up of 13.8 months (range 0.2-37.4 months), the median OS has not yet been reached among frontline treated patients at 12 ng/kg/day dosing.21

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Mind Over Matter: One Person’s Journey From Patient to Change-Maker

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 18 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.

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

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

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

DI: No because it is still too rare.

JK: Are there more people in your country living with the disease now?

DI: 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.

JK: When did you first meet someone else who had SCD?

DI: 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.

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

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

JK: Do you have any siblings?

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

JK: And did your parents know they were carriers of sickle cell trait?

DI: 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.

JK: What part of Africa were they from?

DI: Cameroon.

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

DI: As far as complications, I have nearly everything. I didn’t experience priapism, stroke, or vision 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 three or four times a year with good results, but we decided to stop treatment and use it only when needed. For instance, when I had my ileus we used it, as well as during a pain crisis. But I haven’t had a major crisis for about 10 years now, I still have some manageable pain maybe once a year when I push a little too hard.

JK: That’s amazing! To what do you attribute that improvement?

DI: Many things. I didn’t have any more [successful] treatment options so I was 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.

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.

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.

JK: Do you take any medicines now?

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

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 have helped me a lot, but over time I have also learned to automate it in my brain, as well as lots of daily practice.

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

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

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

DI: 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 understood the patient side and the caregiver side [of health care]. 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 and Norway because they were quite advanced on these issues compared to the rest of the world.

JK: What kinds of technologies are you working on?

DI: We are working on a health information system that is able to collect any kind of exposure health data. We are focusing on data that can be easily collected with the need for additional expensive sensors. We can get data from smartphone step-counters, environmental data such as pollutants and temperature, or other self-reported data such as oxygen saturation.

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

DI: 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 interpreted my stories correctly. 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 requested … 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.

JK: 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 you should talk with them in a way that encourages them?

DI: 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.

JK: What else do you want to do in the long term?

DI: 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 being involved in 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 Ph.D 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. For instance, building more research centers, to do more 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 “grown into being a predominant pediatric disease to a predominantly adult disease. While the thalassemia syndromes are heterogeneous, including homozygous or compound heterozygous β-globin detects, the pathophysiology is primarily related to ineffective erythropoiesis and systemic iron overload 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 other agents such as West Nile virus and severe acute respiratory syndrome. 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 has had a major impact on reduction in morbidity. These are agents with a longer half-life than deferiprone, and with the convenience of oral administration, have improved compliance significantly with less iron-related cardiac and endocrinologic dysfunction. The ability to combine chelators offers options for dose reduction for toxicity as well as intensification when required. Until recently, deferiprone was only available as dispersible tablets, and apart from the inconvenient mode of administration, the inactive ingredients also caused gastrointestinal intolerance. The introduction of the tablet form and granule formulation for children will eliminate some of these disadvantages, and likely improve compliance.

Previous reliance on the serum ferritin to guide chelation often resulted in over- or under-chelation since serum ferritin does not reflect total body iron reliably. MRI technology has enabled more accurate quantification of iron in the liver and heart (standard), as well as pituitary and pancreas, allowing superior monitoring and tailored chelation regimens. This is now the recommended standard of care for monitoring iron overload, both in transfusion-dependent and non-transfusion-dependent patients.

Finally, advances in allelogetic hematopoietic stem cell transplantation (allo-HSCT) have resulted in better curative outcomes, with reduced toxicity and fewer long-term adverse effects. Despite these advances, there remain some iron-related needs for further development. Currently, the mainstay of treatment is regular transfusion (for transfusion-dependent patients), regular monitoring for iron overload, and iron chelation therapy when indicated (for both transfusion-dependent and non-transfusion-dependent patients). While allo-HSCT is curative, this option has the best results when the donor is a matched sibling. Only approximately 20 percent of patients have such a donor, and for the remainder of patients, a curative option was a significant need. Novel treatments are now in transitional stages of clinical trials and offer the promise of a cure for a much larger proportion of patients with thalassemia.

Gene Therapy
The development of a gene therapy strategy to “cure” thalassemia has been ongoing for three decades, but only recently have these efforts been moved into the clinic. Advanced lentiviral gene transfer technology has been developed, and clinical trials are ongoing. Results from the Bluebird Bio phase I trials (HGB-204 and HGB-205) in 22 transfusion-dependent thalassemia patients after a median of 26 months of follow-up were recently reported. Patients’ stem cells were collected after stimulation with plerixafor, then transduced ex vivo with the lentiviral vector and reinjected into the bone marrow. Hemoglobin production attributed to the transduced gene ranged from 3.4 to 10 g/dL, with total hemoglobin levels in the 8.2 to 13.7 g/dL range. In the remaining nine patients with β-globin genotypes, the median annualized transfusion volume was reduced by almost 75 percent, and three patients were able to come off regular transfusions altogether. In patients with at least 8 g/dL of hemoglobin from the transduced gene, the vector copy number was 0.6 or greater per transduced cell. The treatment as a whole was associated with only the usual adverse events which would otherwise be expected during autologous SCT. The vector had numerous integration sites, and no clonal dominance was noted. The company then refined the manufacturing process for the vector, and preliminary results from the phase III study (HGB-207) reported at the 2017 ASH Annual Meeting showed further improvements in vector copy numbers and consequently, increased hemoglobin production. While the duration of follow-up at the time of the report was still relatively short, the results were encouraging, and greater transfusion reduction or independence may be anticipated in subsequent reports. Additional phase I/II trials using a lentiviral vector-based gene therapy are currently underway in Italy. Preliminary work has shown encouraging results for other novel strategies including gene editing. Targets for gene editing are diverse, including the BCL11A locus and the β-globin gene locus itself. Techniques used to disrupt BCL11A, nuclease and the use of CRISPR/Cas9.

Activin Trap Agents to Promote Effective Erythropoiesis
Intramedullary hemolysis and ineffective erythropoiesis as a result of imbalance in β and γ-globin chain production is a central part of the mechanism of disease in thalassemia. This results in accumulation of GDF11-producing cells. GDF11, a transforming growth factor β ligand, inhibits differentiation of the erythroid precursors, worsening ineffective erythropoiesis and thus anemia. Novel strategies to trap/bind GDF11 and thus promote more effective erythropoiesis led to the development of two such activin traps, luspatercept (ACE-536) and sotatercept (ACE-011). Luspatercept consists of the extracellular domain of activin βb ligated to the human IgG1 Fc domain and prevents binding of GDF11 to its receptor. The drug, which is administered subcutaneously every three months, has been in clinical trials for the past three years. Phase II trials were conducted in transfusion-dependent and non-transfusion-dependent thalassemia patients. There was significant reduction in transfusion requirements in almost all transfusion-dependent patients (genotypes were not required for entry into the study), greater than 33 percent reduction in 83 percent of patients and more than 56 percent reduction in 67 percent, with several patients achieving transfusion independence. In the non-transfusion-dependent patients, there was a significant increase in hemoglobin levels, more than 1 g/dL, in 78 percent, and greater than 1.5 g/dL, in 56 percent of patients. In both populations, the drug was well tolerated in all patients, with very few adverse events related to the drug. The phase III double-blind, randomized, placebo-controlled, international multicenter trial (BELIEVE) of luspatercept has been completed recently, and results are expected to be published soon.

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 initiatives and that he is committed to supporting 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 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.

Stoner
by John Williams


So why is Stoner not better known by the literate general public, and why is it worthwhile for hematologists to read? Perhaps the main reason Stoner never became “the great American novel” is that Americans like winners. The protagonist of Stoner, in contrast, never advances beyond the merely echoes of mediocrity, despite talent and the best of intentions.

William Stoner was born on a hardcrops farm in 1891 and left home in 1910 to study at the University of Missouri. While at school, he fell in love with literature, beginning with Shakespeare’s 73rd sonnet, which prompted an “epiphany of knowing something through words that could not be put in words.” He became an assistant English professor at the university, much to the disappointment of his parents, who had naively hoped he would return to the family farm.

Professor Stoner worked hard but married badly — not quite as disastrous a match as Tertius Lydgate’s Rosamund in Middlemarch, but rotten enough that his wife conspired to estrange him from their daughter, the one person Stoner loved unreservedly. He never learned to play academic politics; at the university, was thwarted at every step by a departmental rival, Hollis Lomax, who bore a grudge after Stoner refused to pass Lomax’s pet graduate student whose ignorance was exposed in an oral examination.

In middle age, Stoner found love with a bright graduate student who shared his passion for language. But his academic enemies managed to drive her off and end their relationship. His academic focus turned out to be a dead end, his few publications were rarely cited, and after his death from cancer, he was quickly forgotten, memorialized only by a medieval manuscript that a few of his more sympathetic colleagues quietly donated in his name to the campus library.

The novel is unflinching in its portrayal of life as it is usually lived, with all its shabbiness and frustration, which makes for painful reading at times. Let’s face it: For most of us, our careers will not turn out quite how we envisioned at age 21. There will be disappointments, rejections, and failures, much of which will be out of our control.

As Cornell economist Robert Frank wrote in Success and Luck: Good Fortune and the Myth of Meritocracy, being talented and hardworking is never enough to guarantee success. Luck, or what the ancients might call fate, karma, or destiny, plays an essential role. In a 2010 Time cover story, Tom Hanks praised Stoner as one of his five favorite books — perhaps not a surprise for the actor who played Forrest Gump. Lefty Gomez’s famous quote, “I’d rather be lucky than good,” applies to medical doctors just as much as baseball pitchers.

Despite his lack of external validation, Professor Stoner’s passion for literature and for teaching English were ends in themselves. In the same way, our own devotion to our field — for caring for the sick, teaching the next generation of hematologists, and discovering how blood behaves in health and disease — can keep us going through lean times when the world sees indifference or even hostility as ruthless but also tender, and shows that there can be value even in a life that seems unfulfilled.
Microbial Signals May Drive Leukemia Development in Subjects With Clonal Hematopoiesis

I
t is well understood that only a proportion of patients 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 developing myeloid malignancies.1,2 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 hematologic malignancy (e.g., patients with ASXL1 mutations have a higher risk of developing myelodysplastic syndromes (MDS), while 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 infective disease was associated with a 1.5-fold increased risk of AML (OR, 1.3; 95% CI, 1.2-1.4).)3 Additionally, prior work in mice has demonstrated that systemic administration of a TLR2 agonist acts as a trigger for the development of acute myeloid leukemia or myelodysplastic syndromes. The authors identified that administration of TLR2 agonists (cell wall components of several Lactobacillus strains) induced extensive myelopoietic differentiation in Tet2 KO mice but not littermate controls. Similarly, treatment with mice of dextran sodium sulfa (DSS), a compound known to alter intestinal barrier function, was shown to increase the risk of 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 develops overt myeloid malignancy, and the factors that dictate development of myeloid malignancy in Tet2 knockout (KO) mice are not well understood. The authors identified that administration of TLR2 agonists (cell wall components of several Lactobacillus strains) induced extensive myelopoietic differentiation in Tet2 KO mice but not littermate controls. Similarly, treatment with mice of dextran sodium sulfa (DSS), a compound known to alter intestinal barrier function, was shown to increase the risk of development of myeloid malignancies from a clonal hematopoiesis state driven by Tet2 deficiency. 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 dissimilation 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 expression 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 result from dysfunction of the small intestine barrier are critical for development of myeloid malignancy in Tet2 KO mice. Interestingly, the authors also noted that mice with Tet2 deletion in hematopoietic cells appeared to have a dysfunction of small intestinal barrier and increased systemic translocation of bacteria. How much tumors in hematopoietic cells could impact intestinal barrier function in this way is not clear and why it likely be the subject of future work by this group. It will also be interesting to identify whether such gut dysbiosis occurs in human subjects with clonal hematopoiesis. Nonetheless, from a therapeutic perspective, these findings suggest the interesting possibility that blocking inflammatory bacterial signals in clonal hematopoietic cells could reduce risk of developing leukemias. Add in, 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 also be interesting to evaluate whether serum inflammatory cytokines may correlate with clone burden and risk of myeloid malignancy development in subjects with clonal hematopoiesis.


Table. Possible Reasons for Direct Oral Anticoagulant (DOAC) Level Testing in Clinical Practice

1. Unexpected bleeding on a DOAC
2. New thromboembolic event on a DOAC
3. Suspicions for DOAC overdose
4. Suspicions for non-adherence
5. Echocardiogram to evaluate left ventricular function
6. Status post bariatric surgery or upper intestinal tract resection surgery
7. Concomitant therapy with a drug that may significantly affect DOAC pharmacokinetics
8. Assessment of efficacy of DOAC therapy in patients with renal impairment
9. Evaluation of sinus rhythm or ventricular function
10. Alethis on long-term anticoagulation therapy wishing to engage in contact sports

In this study, the researchers observed 456 consecutive patients with atrial fibrillation (AF) newly started on a DOAC. They performed DOAC-specific measurements. These included detection of thrombin formation time and antithrombin level, and correlation with patients who experienced thromboembolic and anti-Xa level variability. Do Plasma Levels of Direct Oral Anticoagulants Correlate With Hemorrhagic and Thrombotic Complicats?


Direct oral anticoagulants (DOACs) are administered in fixed doses without routine anticoagulant monitoring. There may be an occlusal reason to check peak and/or trough drug levels at least once in 12 months. Do plasma levels of direct oral anticoagulants correlate with hemorrhagic and thrombotic complications of direct oral anticoagulants? A variety of anticoagulant-specific measurements were performed, including drug level testing, which may allow safer and more effective use of the DOACs. For each NOAC, the C-trough range from the limit of quantification to the highest value was subdivided into four equal classes, and results were attributed to those categories. Thromboembolic complications occurring during one year of follow-up were recorded. The main finding was that the incidence of thromboembolic events among patients with DOAC C-trough levels in the lowest quartile was 2.4 percent and in the remaining three groups, 0 percent. The patients with thrombotic complications also had a higher mean CHADS2-VASc score than the trough-corrected population (p=0.05 [95% CI, 0.9-3.8 vs. 3.2 [95% CI, 0.9-3.1]). Thrombotic events occurred only in DOAC-treated AF patients who had low plasma trough levels with a relatively high CHADS2-VASc score.

This publication does not have any impact on my current clinical practice. However, the type of study and future dose adjustment studies may eventually allow us to identify patients at high risk for DOAC-associated adverse outcomes in whom DOAC-level driven individualization of dosing might allow safer and more effective use of the DOACs.
The Hematologist: Dr. Yannakou and Dr. Roberts indicated no relevant conflicts of interest.


Not All Large Cells Are Created Equal: Is Genomic Classification the New Frontier in B-cell–like (GCB; 28.6%), and unclassified (20.0%).

Furthermore, the advent and increasing use of massively parallel sequencing (MPS) has implicated somatic alterations in a large number of genes in the pathophysiology of DLBCL. Unfolding, however, genomic landscape studies have been either insufficiently powered or have lacked the clinical annotation required to comprehensively define clinical-pathological subgroups within the heterogeneously 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 gene alterations onto cell-of-origin categories defined by gene-expression profiling. A total of 974 prospectively collected and frozen DLBCL samples underwent comprehensive, multiplex genomic analysis (whole-exome, targeted amplicon and transcriptome 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 unclassified (25.0%).

Numerous alterations either by somatic mutaton and/or copy number variation (CNV) were significantly differentially distributed among the three cell-of-origin categories defined by gene-expression profiling. A total of 734 prospectively collected and frozen DLBCL samples underwent comprehensive, multiplex genomic analysis (whole-exome, targeted amplicon and transcriptome 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 unclassified (25.0%).

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 alteration 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 in many of those unclassifiable by cell of origin.

In the MCD subgroup, dysregulation of p38 mitogen-activated protein kinase and tumor suppressor gene loss, immune editing, HK-2 cell energy, and an HIF-1 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, and expression of germinal center homing, immune editing, enhanced JAKSTAT, and P53 kinase signaling, as well as a GCB-like TCF3-mediated GCB gene-expression profile. The other two genomic subgroups are characterized by NOTCH gene mutations and expression signatures. However, NOTCH1 mutation and/or expression signature (which characterize the N1 subgroup) and mutant NOTCH2 (which typifies the BN2 subgroup) and the related gene SREBP were mutually exclusive, suggesting distinct pathophysiology. The BN2 subgroup was enriched for NOTCH and NF-kB pathway aberrations while the N1 subgroup contained aberrations affecting B-cell differentiation, which may account for the plasma-cell and quiescent-cell gene-expression signature observed in this subgroup.

Clinical outcomes data were available in 240 cases of untreated DLBCL receiving R-CHOP or similar chemotherapy. 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 experiencing significantly superior survival rates (85% and 68%) for 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 for 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 genotypically classified. However, a comprehensive clinicogenomic classifier that considers the IPI, cell-of-origin, and genomic subtyping concurrently is likely to provide the most 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 (dbclavaelab.org).1

The significance of defining distinct genomic subgroups reaches well beyond the predict of response to first-line chemoimmunotherapy. The significant risk of relapse in DLBCL, especially in patients with high IPI scores, necessitates the pursuit of not only selected new therapies. For example, Bruton tyrosine kinase inhibitors such as Brutinib are reported to have significant efficacy in ABC DLBCLs with both MYD88 L265P and CD79B mutatons. The assocaiton of these aberrations with the MCD subgroup, together with the higher frequency of aberrations involving the B-cell receptor-dependent NF-kB pathway in the MCD and BN2 versus N1 and EZB subgroups, implies potential differential response to BTK inhibiton across the genomic subgroups.

The consistion of genomic subgrouping in the design of future trials of targeted agents in DLBCL may allow for the risk selection of patients most likely to derive benefit. Why controls of “all-comers” may prove to be negative, those enriched for patients with the appropriate background may potentially pave the way for a therapeutic paradigm shift in this disease. However, caution is warranted as not every actionable mutation is likely to 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 OREGPRA-based knockouts of certain targetable lornons 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 classifier of a greater proportion of cases and to lower the practical barriers to accessing sophisticated, real-time genomic testing outside highly specialized academic settings.


Figure. Progression-free and Overall Survival Among Patients With Genetically Classified Tumors


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Costas K. Yannakou, MBBS(Hons.), and Andrew Roberts, MBBS, PhD
Dr. Yannakou and Dr. Roberts indicated no relevant conflicts of interest.
diffuse large B-cell lymphoma (DLBCL) represents a heterogeneous collecti-on of lymphomas with varied prognoses and clinical outcomes. Up to 60 percent of patients are cured with upfront chemotherapy, leaving 40 percent of patients having not responded to or relapsed after first-line treatment. The internal-na-tional prognostic index (IPI) score, which is based on certain patient and clinical characteristics, can differentiate between low-, intermediate-, and high-risk groups.1 Gene-express-profi-yzing of DLBCL identifies three distinct subgroups—germinal center B cell-like (GC), activated B cell-like (ABC), and type 3, all with different outcomes.2-4 GC lymphomas have a significantly improved prognosis over ABC and type 3 lymphomas. This is interesting because another high-risk factor, lymphomas that harbor translo-cat-translocating the MYC gene on chromosome 8 as well as a second gene (most commonly BCL2 on chromosome 18), or so-called “double-hit” lymphomas, are almost exclusively of the GC subtype.5 This distinct-ABC and type 3 subtypes, is incomplete. Dr. Bjorn Chapuy and colleagues analyzed 304 primary, newly diagnosed DLBCL clones by whole-exome sequencing, with an expanded dataset to also identify structural variants and somatic copy number alter-la-tions. This analysis led to refinement of our current understanding of the genetic and molecular subtypes of DLBCL and has implications for the diagnosis of treatment trials in this cohort of diseases.

Dr. Chapuy and colleagues identified nearly 100 candidate cancer genes that are recurrently mutated in DLBCL, as well as the most commonly rearranged genes and areas of chromosomal copy number gain or loss, leading to copy number gain or loss of identifiable driver genes. On average, tumors in this series had alter-la-tions in 17 driver genes, with a total of 158 distinct alter-la-tions identified. Using non-negative matrix factori-zation consensus clustering, five distinct genetic subtypes of DLBCL were identified (C1-C5). A sixth subtype, C0, had no detectable alter-la-tions. C1 and C5 were largely composed of ABC DLBCLs but differed from each other with respect to prognosis and genetic alter-la-tions. C5 lymphomas, alternately, did quite a bit better with R-CHOP than C3 lymphomas and other ABC subtype lymphomas; long-term PFS was seen in nearly 70 percent of these patients. Similar to the C3 group, these lymphomas frequen-tly had TP53 and NOTCH2 mutations, and 70 percent of patients remaining alive and free of relapse with prolonged follow-up. These lymphomas had muta-tions in core histone genes as well as in genes involved in immune evasion, the B cell receptor/PI3 kinase pathway, and MYC translocations. This genomic signature was reminiscent of marginal zone lymphoma, perhaps indicating that these lymphomas transfor-ma-tions from a pre-existing unmalignant marginal zone lymphoma, or that they arose from an extracellular or marginal zone origin. C3 and C4 lymphomas, alternately, were largely GC-like and BCL6. C4 lymphomas had a relatively good prognosis, as expected for GC lymphomas, with nearly 70 percent of patients remaining alive and free of relapse with prolonged follow-up. These lymphomas had core histone and immune evasion mutations as well as MYD88 and EZH2 mutations. These lymphomas were associated with alterations in R2B2 and muta-tions in chromatin remodeling genes such as EZH2 and CREBBP. These muta-tions are frequently seen in follicular lymphoma, suggesting that like C1, C3 lymphomas may represent transforma-tions from a pre-existing benign follicular lymphoma.

This analysis is being reported simultaneously with that of the group from the National Institutes of Health (NIH), who identified four distinct genomic DLBCL subgroups using exome and transcriptome sequencing, array-based DNA copy number analysis, and whole-exome sequencing. The EBZ subgroup and EZB subgroups with muta-tions in MYD88 and CD79B, and alter-la-tions in EZ2H and CREBBP, corresponded with the C5 and C3 subgroups in the Dr. Chapuy study, respectively. Interestingly, while both the MCD and C5 subgroups did similarly poorly with R-CHOP chemotherapy, the EBZ and C3 subgroups, which genetically seem similar, seemed to have divergent outcomes. The EBZ subgroup had super-normal, and relatively good outcomes compared with the C5 subgroup. The NIH group also identified a fourth subgroup, C6, which was comprised of lymphomas with concurrent BCL2 and muta-tions in NOTCH2, the C4 subgroup, which was similar to the C1 subgroup. This group was more frequently included in both GC-like BCL6 lymphomas and ABC lymphomas, but was distinct from C5 lymphomas. These groups were similar, however, with respect to outcome following R-CHOP chemotherapy. Finally, the NIH group identified a fifth subgroup, BM2, which was a hybrid of both the GC and type 3 subtypes, with a less than 50 percent of patients remains alive and free of relapse with prolonged follow-up. Double-hit lymphomas were found in both C2 and C3 lymphoma subgroups.

This knowledge is helpful for several reasons. First, when a classification of the recurrent genetic alter-la-tions is reassuring in that we are closer to defining distinct B-cell logic and genetic subtypes of DLBCL. Regardless of which group is correct in terms of prognosis, the identifi-ca-tion of the same cluster of driver genes in patients allows for the ta-yoring of therapy to target these recurrent genetic alter-la-tions and to improve outcomes for all.

4. Schmitz/Staudt MCD MYD88, CD79B 10
Venous Thrombosis on One Side and Bleeding on the Other: How to Walk the Fence in Cancer Patients With Thrombosis and Thrombocytopenia


People with cancer are at high risk for developing venous thromboembolism (VTE). Unfortunately, they are also at high risk for bleeding, particularly in the context of thrombocytopenia. When a patient with severe thrombocytopenia (50 × 10⁹/L) develops VTE, walking the fence between recurrent thrombosis and bleeding can be daunting. The Internal±external Society of Thrombosis and Haemostasis ISTH Scientific Subcommitte recently published an article that offers clinicians guidance on how to manage this difficult situation.

First, it is important to realize that there are no randomized controlled studies evaluating the safety and efficacy of anticoagulant therapy in patients with cancer who have thrombocytopenia. Instead, the data are limited to case series and small observational cohort studies. For this reason, the ISTH article provides guidance statements instead of graded recommendations.

1) Age of VTE

The natural history of venous thrombosis tells us that the risk of extension and/or embolization is highest in the first 30 days. Consequently, the need for therapeutic anticoagulant therapy is critical during this time frame. After 30 days, the risk of major bleed is likely.

2) Location andExtent of VTE

Proximal lower-limb deep vein thrombosis (DVT) is considered more severe than catheter-associated upper-limb DVT owing to the higher potential for clinically significant pulmonary embolism (PE) travelling from the larger caliber veins within the lower limbs. Similarly, PE located within the main, lobar, or segmental pulmonary arteries is more of concern than subsegmental PE. While JAK2 inhibitors do not lyse existing emboli, they reduce the likely 30-day risk.

3) Cancer-associated Thrombosis

The authors speculate that the mechanism of disease may potentially reflect the ability of ruxolitinib to reduce T-cell function and numbers with lymphoma developing in patients. The authors then demonstrated this association between hyperplasia and B-cell transformation with subsequent increased risk of aggressive B-cell lymphoma development.

4) Risk-Benefit Analysis

While JAK inhibitors have proven to be an effective treatment for patients with myelofibrosis, this work provides compelling evidence that treatment may come at a cost of increased risk of aggressive B-cell lymphoma development. Why? The authors speculate that the mechanism of disease may potentially reflect the ability of ruxolitinib to reduce T-cell function and numbers with lymphoma developing in patients. The authors then demonstrated this association between hyperplasia and B-cell transformation with subsequent increased risk of aggressive B-cell lymphoma development.
Circulating Tumor DNA in Lymphoma Monitoring

(Cont. from page 1)

stage (III, IV, or I or II with bulky disease, or IIB; p = 0.001), and German Hodgkin Study Group Score favorable versus intermediate and unfavorable risk groups (p = 0.013).

Mutat=ns 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 as well as the concurrent study by Dr. Enrico Tiacci and colleagues (32% of cases). Two hotspot mutat=ns in STAT6 (p.N417Y and p.D419N/H/A) among other variants are all located in the DNA binding domain and seem to support growth of cHL cells in a manner similar to JAK inhibitors. 

Other recurrent pathways included the NF-kB (46.2% of cases), PI3K/AKT (48.2%), epigenetic (35.0%), immune surveil(lance (27.5%), and NOTCH (20.0%) pathways. This pathway distribution is distinct from DLBCL, but sim/Yar to that seen in primary medullary large BCL.

cDNAs reflects two different paths of clonal evolut=on in the setting of refractory disease in cHL. Interestingly, refractory cases that received chemotherapeutic therapy retained their founder clones (predominantly STAT6, TIFA/P, ITK/P, and NOTCH3) with acquisition of new subclonal events, resulting in a trend toward an increased percentage of mutat=ns in genes such as ARID1A, TET2, BCROR, SPEI, EP300, KMT2D, and XPO1 (Figure 1A). By contrast, those patients who received immunotherapy ef=ectively cleared their founder clones with emergence of new clonal events (Figure 1B).

cDNAs predicts response to therapy in cHL. 

Sim=ar to ppr= studies in DLBCL, the researchers suggest an optimized cutoff of a two-log reduc=on in cDNAs load in response to chemotherapeutic agents 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 cDNAs may complement (or even ultimately replace) PET/CT monitoring.

In summary, this study showcases the utility of cDNAs monitoring in cHL. This methodology highly correlates with the tumor genetics and burden, measures only the neoplastic cells and not the background inflamm=ary=related, elucidates tumor burden, and predicts outcome. In a disease where both morphologic and radiographic methods largely measures the inflammatory component of cHL and not the tumor burden. These results suggest that cDNAs may complement (or even ultimately replace) PET/CT monitoring.


Figure A.

Chemotherapeutic Therapy

Figure B.

Immunotherapy

Figure C.

(A) Schematic of clonal evolut=n in cHL after chemotherapeutic therapy as determined by cDNAs analysis, with resurgence of the founder clone. (B) Schematic of clonal evolut=n in cHL after immunotherapeutic therapy as determined by cDNAs analysis, with emergence of new clone(s). (C) Reduc=on in cDNAs burden correlates with likelihood of complete response. (Reprinted from Spina V, Brusco=gn A, Cuccaro A, et al. Circulating tumor DNA reveals genetics, clonal evolut=n, and residua disease in classical Hodgkin lymphoma. Blood. 2018;131:2413–2423.) In this situation, the damaging effects of UVB were create sunburn in a fair-skinned person. The wild-type 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 product=on. As further experimental evid=ence for the protective effect of the melanocyte cover, simYar findings were observed when melanin product=on was m=activated. A further experimental innov=ation 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 situ=on, the damaging effects of UVB were seen even in the wty-type animals, indicating that the anatomical orient=on= of the melanocytes is critical.

Comparative studies in many other fish also revealed melanocytes covering the hemopoietic 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 demonstr=on 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 protect=n against UVB-induced damage.

Tissue stem cells are the crown jewels of somatic organs, and evolut=n has provided them with unique levels of protect=n. The import=ance of this is shown by the extreme sensitivity of human HSPCs to UVB in vitro, where much smaller doses than those used in this study can completely suppress colony-forming potential. The bone marrow has provided a protective niche to sustain hemopoiesis during the conquest of the land. Hematologists can finally gain some closure on one of the most perplexing quest=ns in their discipline.

The Hematologist: ASH NEWS AND REPORTS


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Dr. Moss indicated no relevant conflicts of interest.

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Dr. Zhang indicated no relevant conflicts of interest.
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), the American Society of Hematology (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 Chesser to serve on the ASH staff as director of the Sickle Cell Disease Clinical Trials Network. He will be responsible for the network’s creation, implementation, and effective operation. Under his purview, the network will focus on infrastructure, programs, and services to help overcome the challenges of conducting clinical trials in SCD patient populations. This includes advancing patient engagement strategy to increase understanding of both the disease and clinical trials overall.

In this Q&A, Dr. Chesser explains more about his role and the direct-n of the network in the near future.

Q: Describe what inspired you to join ASH to lead the CTN?

A: SCD was first described in the scientific literature more than 100 years ago, and although it was the first “molecular disease” identified (in 1961 by Dr. Linus Pauling), there are still only two approved drugs for its treatment. These are exciting times in SCD research, and the goals of the CTN couldn’t be more admirable. I was inspired by ASH taking a leadership role in this area to improve the lives of patients living with SCD.

Q: Can you share with our readers some of the history of the network?

A: In 2014, ASH leadership called for increased commitment to this global SCD burden. As a first step in the development of this initiative, ASH hosted the Sickle Cell Disease Summit to develop strategies for improving outcomes for individuals living with this devastating disease. The summit defined SCD as a multichronic condition consisting of both a genetic component (prominent in individuals of African descent) and a social obligation to the state, society, and global issues related to SCD. In the research and clinical trials area, the SCD CTN Task Force was created under the leadership of Dr. Charles Abrams and Edward Benz, with the goal of identifying the scope, goals, and high-priority research objectives for the CTN. In the past year and a half, the task force has received feedback and advice from SCD clinicians and researchers, CTNs in other disease areas, leaders of pharmaceutical and biotech companies, and the National Heart, Lung, and Blood Institute (NHLBI) to address the need for a CTN for SCD. In May 2018 the SCD CTN was approved by the ASH Executive Committee to address research and clinical trial needs. Moving quickly, we have hired a new executive to lead the ASH CTN, and my first day on the job was in July.

Q: What makes SCD such a high-value priority in the clinical trials space?

A: The simplest explanation is that there are now more than 40 new drugs in development to treat SCD, yet there is no cohesive path forward for recruiting and retaining the number of patients needed to determine which drugs will be the most beneficial to individuals living with SCD.

Q: In your view, what is the core of the CTN? What will hold it together and act to fuel its success?

A: Entering the initial phases of forming the SCD CTN, we are ensuring that the network’s foundation is built on a strong scientific basis with patients, caregivers, and clinicians involved to form a collaborative relationship between patients, their caregivers, patient advocacy groups, physicians, and academic and industry stakeholders.

Q: Now that you are on board here at ASH, what can we expect to see in the coming months?

A: The next steps will be to advance the following four areas in establishing the SCD CTN:

- Patient engagement. We are preparing a request for proposals to engage with a firm that will assist ASH in discussions with the community so that we can develop a long-term partnership that is grounded on mutual trust and collaboration.
- Governance. We are examining the best structure for the CTN so we can engage an organization with the appropriate inputs and without undue bureaucracy.
- Sites. We need the appropriate blend of both pediatric and adult sites for enrolling patients. We will be soliciting proposals from sites before the end of the year.
- Industry engagement. We will work with the patient and scientific communities to prioritize research needs and collaborate with industry to see how we can all match those priorities.
- Q: What is your message for members who would like to get involved and help spur progress in the area?

A: As we start to build this network, we want to hear from the SCD stakeholder community, especially those who are interested 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 SCDCTN@hematology.org.
Other secondary outcome measures include, but are not limited to, pregnancy-induced hypertension, pre-eclampsia, placental abruption, and maternal and perinatal death. A total of 200 women are expected to be randomized to the intervention group and 200 women to the control group. The primary outcome measure will be the perinatal mortality rate, defined as the number of stillbirths or neonatal deaths per 1000 total deliveries. Secondary outcomes will include occurrence of at least one vaso-occlusive complication lasting more than 24 hours during pregnancy and 30 days postpartum, respectively.

Rationale: 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 10.19 [95% CI, 3.46–34.11] vs. 3.76 [95% CI, 2.34–6.46]), respectively.1,2 Figures 1 and 2. Pregnancy women with SCD have higher rates of adverse maternal and fetal complications including, but not limited to, pre-eclampsia and intrauterine growth restriction (pooled OR, 2.05 [95% CI, 1.47–2.85] vs. 2.79 [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-altering complications of pregnancy in women with SCD.3

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.4 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.5 The primary outcome is the cancellation subscore from the Wechsler scales. Secondary outcomes include, but are not limited to, general cognitive functioning, quantitative brain MRI, quality of life, and daily pain via a smartphone App (GomedSolutions, Inc).

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)

STUDY DESIGN: This is a phase III randomized study of adding iomab-B, a monoclonal antibody directed at CD55 and linked to radioisotope iodine-131, to a reduced-intensity conditioning (RIC) regimen and protocol-specified allogeneic hematopoietic stem cell transplantation (ASCT) for patients with relapsed or refractory acute myeloid leukemia (AML) older than 55 years.

ACCURAL GOAL: 150 patients

PARTICIPATING CENTERS: 16 centers around the United States

STUDY TITLE: 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 (such as whole-body radiation) during conditioning. This puts them at high risk for post-transplantation relapse.

Rationale: Strategies that have tried to increase the intensity of preparative regimens may increase non-reapse mortality. This study incorporates targeted marrow ablation with a CD55 monoclonal antibody conjugated to the radioisotope 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 increased risk of relapse and death in patients with AML.4,5 It is unclear whether even myeloablative conditioning can overcome inadequate disease control.6 And what about patients with comorbidities? Reduced-intensity transplantation, which banks 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 option 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 reinduction.4 A second approach is the use of mutation-directed agents such as incorporating therapy targeted against the Fas-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-CD45 antibody.7 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 non-relapse causes by day 100, and the overall relapse rate was 40 percent at one year. A similar study of 16 patients younger than 50 years was published in 2014.8 Both were aimed at finding a maximal-tolerated dose of the 131I-BC8 AB, now called “lomab-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 lomab-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 induction of donor T cell 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 allograft 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 investigative priority.


Laura C. Michaels, MD

Dr. Michaels indicated no relevant conflicts of interest.
A Transplant Patient With Visual Disturbance

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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 exam revealed 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

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

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 hematologic 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.