The San Diego Convention Center lights have dimmed, the banners are down, and another of our yearly rituals has wrapped up for the year. For those of you who were able to attend the 2018 Annual Meeting in San Diego, I hope you found it as exciting as I did. I remember crafting my fellowship essay nearly two decades ago, writing that I wanted to enter a field that was on the precipice of change. Cannot even the most cynical of us look at the upward trajectory of care in the diseases we treat without some modicum of awe and excitement? There were nearly 30,000 attendees at last year’s annual meeting, all there to learn from and to some degree celebrate these collective accomplishments.

As the new year starts, The Hematologist is going to toast some of the past year’s advancements — those highlighted at the meeting or published during 2018. This is a tradition started by former Editor-in-Chief Dr. Jason Gotlib, and it has proven to be both popular and helpful to readership. As a team, our editorial board has selected 11 developments from 2018 that we feel represent true breakthroughs that made 2018 a big year in the field.

To me, the 2018 ASH Annual Meeting felt different. It had a fresh and energetic vibe. The member-centric emphasis of the meeting was evident. From the get-go, the brilliant idea of registration and materials pickup at the airport was a Twitter sensation. It was clear that attendees also appreciated the thoughtful inclusion of Alexa-Ask ASH in Japanese, the Expressions of Clinician Wellbeing art exhibit, ASH Assist, and free collaboration rooms, among other great amenities. The evolution of Trainee Day into the fun-filled ASHa-Palooza just before the official annual meeting kickoff really set the stage for a memorable meeting.

The quality of data presented at this year’s meeting will inform our practice for years to come. The scientific and education program sessions were carefully planned to meet the needs of a variety of disciplines nested under the vast field of hematology. The Global Capacity-Building Showcase touted the Society’s international collaborations in the form of fostering growth in low- and middle-income countries. The well-attended ASHFAA (U.S. Food and Drug Administration) Joint Symposium on New Drug Approvals featured drugs with recent approvals to treat blood disorders, coupled with the FDA’s insight into the drug approval process. New this year, ASH President Dr. Alexis Thompson delivered a State-of-the Society address and shared her insights on the many ways in which ASH works on behalf of its members to advance the mission of “helping hematologists conquer blood disease worldwide.”

Sunday’s Plenary Scientific Session lived up to its promise. We learned about luspatercept, a novel drug that was shown to significantly reduce transfusion requirements in adult patients with very low-, low-, or intermediate-risk myelodysplastic syndrome with ringed sideroblasts in the MEDALIST trial. In the landmark REACH trial, hydroxyurea was shown to significantly increase hemoglobin concentrations and reduce veno-occlusive crisis and chest pain syndrome in patients with sickle cell disease (SCD) in African countries. Thanks to this session and the research performed in Krause Lab at Yale University, hematologists now finally know why platelet counts are elevated in patients with iron deficiency anemia (Bring it on, students/residents and fellows!). Another study with immediate practice implications was the Alliance A041202 randomized trial, which revealed two key messages. First, the addition of rituximab to ibrutinib in patients with chronic lymphocytic leukemia (CLL) does not add to the duration or depth of disease response. Additionally, rituximab improved progression-free survival (PFS) compared to bendamustine and rituximab combination therapy, ushering in an era of chemofree frontline therapies in CLL. To learn more about these and other plenary abstracts please visit the newly launched ashenewsdaily.org and look for coverage from the December 3 (Monday) issue.

(Cont. on page 6)
Celebrating Our Strengths in 2019

It is a great honor for me to step into the role of ASH president, following in the footsteps of a lineage that now dates back 60 years! I am grateful to immediate Past President Dr. Alexis Thompson, who provided outstanding leadership to the Society in 2018 and who thankfully will continue to be involved in ASH initiatives. I am also grateful to our talented ASH staff who provide an incredibly high level of support to our officers, executive committee, editors, committees, and members, and to our members who remain devoted to our mission of furthering advances in research, education, and clinical care of hematologic disorders. This year of time is indeed a whirlwind, as we move quickly from Thanksgiving (for those of us who live in the States), to the ASH annual meeting, and then into the holiday season culminating with the turning of the calendar to the new year. It is an appropriate time to reflect on accomplishments and to strategize on priorities for the coming year. This issue of The Hematologist is always my favorite, as our contributing editors look back on the most important scientific and clinical accomplishments in the fields of hematology and our ASH News Daily editor reflects on the highlights of the annual meeting.

As a hematologist who specializes in the care of adult patients with “nonmalignant” blood disorders and has devoted 35 years to pursuing research in thrombosis and vascular biology, I found the annual meeting this year in San Diego to be inspiring. Advances in clinical science related to treatment and prevention of cancer-related thrombosis, novel gene and immuno-therapy approaches to hemophilia, and the release and publication of six of the 10 ASH-sponsored evidence-based clinical guidelines for venous thromboembolic disorders created quite a buzz. Additionally, we heard basic science presentations showcasing breakthroughs connecting the coagulation system to innate immunity and neurodegenerative disorders — a highlight for me. The commitment of our Society to the hemostasis and thrombosis community is strong and was made obvious by the many networking opportunities offered, starting with ASH-a-Palooza at Petco Park and concluding with the first annual hemostasis/thrombosis community reception on Monday evening following the Special Symposium on the Basic Science of Hemostasis and Thrombosis. This took place on the terrace overlooking the harbor and provided an opportunity for trainees, clinicians, and researchers to interact in a casual venue.

2019 promises to be an exciting year for ASH. We anticipate the release of additional evidence-based clinical practice guidelines, including the “final four” for VTE, as well as continued progress on major initiatives, especially in precision medicine, sickle cell disease (SCD), and immunotherapies. Our registry project, now under the banner of the ASH Research Collaborative, is expected to advance efforts to create data hubs for multiple myeloma and SCD, and to establish a clinical trials network for SCD. ASH continues to expand globally as we welcome our first ASH councillor representing international members, host our first Highlights of ASH in the Mediterranean meeting in Athens, continue to invest in capacity building in low-income regions, and push forward on our newborn sickle cell screening efforts in sub-Saharan Africa. I look forward to keeping you informed of our progress during the coming year.

I am grateful to immediate Past President Dr. Alexis Thompson, who provided outstanding leadership to the Society in 2018 and who is a great honor for me to step into the role of ASH president, following in the footsteps of a lineage that now dates back 60 years! I am grateful to immediate Past President Dr. Alexis Thompson, who provided outstanding leadership to the Society in 2018 and who thankfully will continue to be involved in ASH initiatives. I am also grateful to our talented ASH staff who provide an incredibly high level of support to our officers, executive committee, editors, committees, and members, and to our members who remain devoted to our mission of furthering advances in research, education, and clinical care of hematologic disorders. This year of time is indeed a whirlwind, as we move quickly from Thanksgiving (for those of us who live in the States), to the ASH annual meeting, and then into the holiday season culminating with the turning of the calendar to the new year. It is an appropriate time to reflect on accomplishments and to strategize on priorities for the coming year. This issue of The Hematologist is always my favorite, as our contributing editors look back on the most important scientific and clinical accomplishments in the fields of hematology and our ASH News Daily editor reflects on the highlights of the annual meeting. As a hematologist who specializes in the care of adult patients with “nonmalignant” blood disorders and has devoted 35 years to pursuing research in thrombosis and vascular biology, I found the annual meeting this year in San Diego to be inspiring. Advances in clinical science related to treatment and prevention of cancer-related thrombosis, novel gene and immuno-therapy approaches to hemophilia, and the release and publication of six of the 10 ASH-sponsored evidence-based clinical guidelines for venous thromboembolic disorders created quite a buzz. Additionally, we heard basic science presentations showcasing breakthroughs connecting the coagulation system to innate immunity and neurodegenerative disorders — a highlight for me. The commitment of our Society to the hemostasis and thrombosis community is strong and was made obvious by the many networking opportunities offered, starting with ASH-a-Palooza at Petco Park and concluding with the first annual hemostasis/thrombosis community reception on Monday evening following the Special Symposium on the Basic Science of Hemostasis and Thrombosis. This took place on the terrace overlooking the harbor and provided an opportunity for trainees, clinicians, and researchers to interact in a casual venue. 2019 promises to be an exciting year for ASH. We anticipate the release of additional evidence-based clinical practice guidelines, including the “final four” for VTE, as well as continued progress on major initiatives, especially in precision medicine, sickle cell disease (SCD), and immunotherapies. Our registry project, now under the banner of the ASH Research Collaborative, is expected to advance efforts to create data hubs for multiple myeloma and SCD, and to establish a clinical trials network for SCD. ASH continues to expand globally as we welcome our first ASH councillor representing international members, host our first Highlights of ASH in the Mediterranean meeting in Athens, continue to invest in capacity building in low-income regions, and push forward on our newborn sickle cell screening efforts in sub-Saharan Africa. I look forward to keeping you informed of our progress during the coming year.
The Hematologist Board of Contributing Editors Welcomes Six New Additions in 2019

This time of the year is full of transitions, and the same holds true for The Hematologist. In December 2018 in San Diego, I expressed ASH’s deep gratitude to five outgoing Contributing Editors: Drs. Omar Abdel-Wahab, Sioban Keel, Paul Moss, and Andrew Roberts. Dr. Abdel-Wahab, with his keen mind and technical experience with the豪华血细胞学和病理学项目，以及纪念斯隆-凯特琳癌症研究中心药物临床试验，为Sickle Cell Disease的专家，凭借超过25年的管理儿童Sickle Cell Disease的专家，凭借超过25年的管理儿童Sickle Cell Disease的经验，凭借超过25年的管理儿童Sickle Cell Disease的经验，凭借超过25年的管理儿童Sickle Cell Disease的经验，凭借超过25年的管理儿童Sickle Cell Disease的经验，凭借超过25年的管理儿童Sickle Cell Disease的经验。她的研究重点是理解在世界中发病的血液病学疾病。DeBaun, the J.C. Peterson Endowed Chair of Pediatrics and director of the Vanderbilt-Meharry Center for Excellence in Sickle Cell Disease, has served as our resident expert in this condition at a time of hope, change, and challenge for these patients.

Dr. Keel has also completed her tenure on the board and will be turning her attention back to her active research career on marrow failure and red cell disorders. Her illuminating contributions to our publications over the past three years have been varied and include one of our top-read articles summarizing best practices in iron supplementation. Also departing after three years on the board is Dr. Paul Moss, a professor of hematology at the University of Birmingham. Looking back over the varied subjects he has tackled during his stint with us — graft-versus-host disease, checkpoint inhibition, bispecific T-cell engager antibody therapy, and CAR-T therapy — I am reminded how much of our work these days lies in manipulating the immune system and how critical his insights have been.

Finally, we say goodbye to Dr. Andrew Roberts, the Metcalf Chair of Leukaemia Research at the University of Melbourne. Dr. Roberts will be turning his talents to one of our sister publications, Blood, as an Associate Editor beginning this year. We will miss his unique ability to simplify the complex — a key talent of great educators.

I can say without hesitation that each of these experts has been critical to the mission of The Hematologist, providing accurate, informed, and interesting insights to the scientific and clinical advancements of our field. When I took this position, I understood how much I would be learning just doing the day-to-day tasks of this job. Having now spent a year reading the work of these folks, I know how silly that was. As I look at what they’ve contributed since beginning their respective tenures — Diffusion articles, feature contributions, or summaries of new clinical trials — I have a wider and richer understanding of our field. I’m sure I speak for many when I give them our sincere thanks.

With each exit, there is an entrance, and we are thrilled that the ASH Executive Committee recently approved the nominations of six new Contributing Editors: Drs. Amy Dezern, Brad Kahl, Steven Lane, Adam Mead, Kristin O’Dwyer, and Iffiyinwa (Ify) Osunkwo.

Dr. Amy Dezern is a hematologist and medical oncologist at the Sidney Kimmel Comprehensive Cancer Center and an associate professor of oncology and medicine at Johns Hopkins University School of Medicine. Dr. Dezern’s primary clinical and research interests focus on chronic myeloid leukemia. Her expertise is in the diagnosis and treatment of myelodysplastic syndromes (MDS), aplastic anemia (AA), and paroxysmal nocturnal hemoglobinuria as well as lymphatic cancers. She is an active participant in clinical trials of diagnostic and therapeutic agents for marrow failure. Dr. Dezern’s research also looks at transplant therapies in AA and novel drugs in MDS. She is the local principal investigator of the MDS Clinical Research Consortium.

Dr. Brad Kahl is professor of medicine at Washington University School of Medicine and director of the lymphoma program at the Siteman Cancer Center. His clinical practice centers on the care of patients with lymphomas and chronic lymphocytic leukemia and his research interests include the development of novel agents for lymphoma, translating biologic discovery, and execution of clinical trials. Since 2009, Dr. Kahl has served as the Chair of the Eastern Cooperative Oncology Group and American College of Radiology Imaging Network Lymphoma Committee.

Dr. Steven Lane is a clinical hematologist at the Royal Brisbane and Women’s Hospital and associate professor at the University of Queensland. He is head of the cancer program and the Gordon and Jessie Gilmour Leukaemia Research Laboratory at the GIMR Berghofer Medical Research Institute. His clinical and laboratory research focuses on the cellular pathophysiology of myeloid blood cancers and the identification and validation of novel therapeutic targets. Dr. Lane is councilor and treasurer of the Haematology Society of Australia and New Zealand and an active member of the Australasian Leukaemia and Lymphoma clinical trials group.

Dr. Adam Mead is professor of hematology in the MRC Weatherall Institute of Molecular Medicine at University of Oxford in the United Kingdom. His research group focuses on understanding how the normal hematopoietic hierarchy is disrupted during the development of myeloid neoplasms. He is the lead clinician for myeloproliferative neoplasms (MPNs) and chronic myeloid leukemia in the Thames Valley Strategic Cancer Network and chair of the MPN clinical study subgroup of the UK National Cancer Research Institute.

Dr. Kristen M. O’Dwyer is assistant professor of medicine and oncology at the James P. Wilmot Cancer Institute of the University of Rochester Medical Center, where she is also the clinical director of the Acute Leukemia Program. Her research focuses on investigating novel therapeutics in acute lymphoblastic leukemia and acute myelogenous leukemia. As a member of the Children’s Oncology Group and the Southwest Oncology Group, she specializes in adolescents and young adults with acute leukemia.

Dr. Iffiyinwa (Ify) Osunkwo is a lifespan hematologist and sickle cell disease (SCD) expert with over 25 years of experience in the management of children and adults living with SCD. She is the medical director of the Sickle Cell Disease Enterprise for Atrium Health (formerly Carolinas Healthcare System) and the Levine Cancer Institute. She is also clinical associate professor at the University of North Carolina Chapel Hill. Her work focuses on improving the quality of life for all persons living with SCD. She developed a nationally recognized model for transition programming for young adults with SCD and established the Comprehensive Sickle Cell Center of Excellence at Atrium.

Thank You to All 2018 Run/Walk Participants and Donors!

The 2018 ASH Foundation Run/Walk took place Sunday morning at the 60th ASH Annual Meeting in San Diego along the Embarcadero. One hundred percent of the registration fees and donations will benefit the ASH Sickle Cell Disease Initiative Fund. The official results of the race are as follows:

- TJ Unger, Top Male 5K
- Faye Sharpley, Top Female 5K
- Jan Trka, Top Male 3K
- Min-Hui Wang, Top Female 3K

The team with the highest number of participants was Janssen Oncology. To see all results and to view the leaderboard, visit www.hematology.org/runwalk. ASH appreciates the generosity of all participants and donors and looks forward to next year’s run/walk, taking place December 8, 2019, in Orlando, Florida.

Thanks to our corporate supporters AbbVie, Amgen Oncology, Freeman, Karyopharm Therapeutics, and Sanofi Genzyme.

Don’t Miss the 2019 Highlights of ASH Series

Obtain a synopsis of the top hematology research presented at the 2018 ASH Annual Meeting. At these more condensed meetings, you will have the chance to evaluate your diagnostic techniques and therapeutic approaches and discuss how new research and clinical updates can be translated into new patient care strategies, with leading hematology experts and colleagues. See below for a location near you:

**Highlights of ASH in North America**
- January 11-12, 2019 — San Francisco and Washington, DC
- January 18-19, 2019 — Chicago and Seattle
- January 25-26, 2019 — Dallas and New York

**Highlights of ASH in Asia-Pacific**
- February 29-24, 2019 — Bangkok, Thailand

**Highlights of ASH in the Mediterranean (New Region)**
- March 15-16, 2019 — Athens, Greece

**Highlights of ASH in Latin America**
- April 5-6, 2019 — Lima, Peru

For more information and to register for these meetings, visit www.hematology.org/highlights.
Among the most important developments in hematology in the past five years is the research into clonal hematopoiesis and aging. In this issue of the *The Hematologist*, Dr. Andrew Dameshek discusses some of the critical research on this topic that was published in 2018 (see page 14). While “CHIP,” “CCUS,” “ICUS,” and others are acronyms that have entered the clinical lexicon, we lack data-driven trials on how to manage these patients. In this No Data Zone, Drs. Bejar and Sekeres present real-world examples of such patients and point out where we, as a community, lack clear consensus on management strategies. Example patient names are fictional.

Charles O. Mattick (“Chip”) is a 68-year-old man with a history of coronary artery disease and recent placement of drug eluting stents in his left anterior descending and left circumflex arteries. His cardiologist sent blood tests following the procedure, which revealed a normocytic anemia with a hemoglobin of 11.4 g/dL, mean corpuscular volume of 90 fL, and red blood cell distribution width (RDW) that was elevated at 17.1 percent. He also had mild iron deficiency and an elevated ferritin level. A coiled angiologist and an aspirin for the stents and had a family history of “leukemia” in his father, he underwent endoscopic evaluation of his gastrointestinal tract and had a myeloid next generation sequencing (NGS) panel assessment performed. While myeloid NGS panels have become more widely available, their use to identify germline cancer susceptibility has not been clearly demonstrated. An example patient, like Chip, has no history of a bleeding ulcer, which was sclerosed, and the NGS panel showed a DNMT3A abnormality with a variant allele frequency of 6 percent. His hemoglobin recovered to a normal range during the next two months, as did his RDW and iron levels. He is referred to a hematologist for follow-up after being told that the NGS report stated that DNMT3A is associated with myeloid malignancies such as myelodysplastic syndromes (MDS), myeloproliferative neoplasms, and acute myeloid leukemia (AML). A bone marrow evaluation shows normal hematopoiesis and cellularity for his age, with a normal karyotype. While at first it might have seemed that Chip O. Mattick had a clonal cytopenia of undetermined significance (CCUS), his anemia was actually caused by bleeding from a gastric ulcer. For conditions that primarily affect older adults, like myeloid malignancies, other causes of cytopenias must be identified. “Response” to agents used to treat conditions such as MDS may be due to resolution of other underlying conditions causing blood loss, as evidenced by measurable response rates in MDS patients enrolled to placebo arms of randomized and studied trials. In a recent trial in which lower-risk MDS patients with ring sideroblasts were randomized to receive luspatercept or placebo, those on the luspatercept had a transfusion independence response rate of 38 percent, while those on the placebo arm had a 13 percent response rate.1

This patient, as his name implies, has clonal hematopoiesis of indeterminate potential (CHIP), a term applied to individuals with hematologic malignancy-associated somatic mutations in the blood or bone marrow, but without other diagnostic criteria for a hematologic malignancy.2 While Chip O. Mattick has a name for his condition (and even an acronym), this may serve only to increase his anxiety for which he has been ill prepared.

Carrying a mutation is associated with increased all-cause mortality (hazard ratio, 1.4), much of which is due to cardiovascular causes, which occurs at twice the rate in people with CHIP. Presumably, cardiovascular events occur through a shared effect on inflammation, localizing to cells of the monocyte-macrophage lineage, and propagation of atherooclerotic plaques.3 Identifying people at increased risk may be helpful, but only if interventions that would consequently increase that risk can also be identified— an area of active investigation.

Lucy Mia and Jeannie Mendelson are sisters in their early 60s with no personal or family history of hematologic disorders. Lucy Mia was diagnosed with anemia and mild leukopenia two years ago when a routine CBC noted her hemoglobin of 10.7 g/dL, a mean corpuscular volume of 98 fL, and a white blood cell count of 3.2 × 10^9/L. She was asymptomatic, but absent a ready explanation for her cytopenias, a bone marrow biopsy was performed. This revealed a myeloid (MGD) with a variant allele frequency of 98 percent dysplasia, no blasts, and a normal karyotype. Her hematologist concluded that she had an idiopathic cytopenia of undetermined significance (ICUS) and ordered an NGS sequencing panel of her peripheral blood. The report listed three variants: an IDH2 R140Q mutation with a VAF of 22 percent, a frameshift in ASXL1 with a VAF of 7 percent, and a DDX1 K381* nonsense mutation with a 53 percent VAF. While mutations in these genes are typical of myeloid malignancies, they are not considered diagnostic and Ms. Mia’s condition was reclassified as a clonal cytopenia of undetermined significance (CCUS), which puts her into a substantially different risk group than our previous example patient.

Patients with ICUS have a high rate of clonal hematopoiesis (~30-40%) indicative of CCUS and early studies suggest that they have a high risk for progression to a frank hematologic malignancy.3 Certain genetic profiles have the greatest risk (10-20% per year) of such somatic mutations in more than one myeloid malignancy driver gene or isolated mutations of a splicing factor gene, AK2, or PRMT5, and have an event risk of 1.3% per year.4 These common CHIP genes, DNMT3A, TET2, and ASXL1, have a more moderate risk of 5 to 10 percent per year. Patients who go on to develop AML often have preceeding clonal hematopoiesis even in the absence of abnormal blood counts. Somatic mutations of IDH1, IDH2, and TP53 may be particularly likely to progress to AML, although in noncytopenic patients, the latency can last many years.5

After a period of relatively stable counts, Lucy Mia develops more profound cytopenias and 5 percent circulating blasts. A bone marrow biopsy is notable for a hypercellular marrow with 40 percent blasts, trisomy 8, and the acquisition of an X;8;Y12 G2D mutation and a second DDX1 mutation (L87T), both with a VAF of 33 percent. She is slated for induction chemotherapy for what is now AML, with a plan to proceed to allogeneic stem cell transplantation. Her sister Jeannie Mendelson is a perfect HLAmatch, but due to occasional mild leukopenia, she has an NGS sequencing panel performed. This reveals the same DDX1 K381* mutation Lucy Mia has with a comparable VAF of 52 percent. A single clone is evident so that this mutation is congenital in both sisters and likely predisposed Lucy to develop AML.6 An alternative stem cell donor is recommended to avoid the potential risk of developing a donor-derived malignancy.

Several somatically mutated genes can be congenitally mutated in some cases. They may not cause early onset of disease, syndromic features, or a recognizable hematologic prodrome. Due to congenital de novo mutations and variants with incomplete penetrance, there may be no suspicious family history as in the case of Lucy and Jeannie. It is important to identify these germline variants as they have implications for family members, especially if they are being considered as potential stem cell donors.7 Instead of the DDX1 K381 variant, Jeannie had been found to carry the same low-abundance, somatic DNMT3A mutation as our first patient Chip, the need for an alternative donor would be less clear. Early data suggest that typical CHIP mutations in donor cells may be associated with adverse outcomes.5 However, larger studies that examine the type and abundance of clonal mutations are needed to better characterize this phenomenon.

For both Charles O. Mattick and Lucy Mia, continued monitoring of blood counts is necessary, with more intensive monitoring for patients who have germline or somatic abnormalities more characteristic of myeloid malignancies, and/or for those with multiple abnormalities. Whether interventions in those with molecular abnormalities typical of myeloid malignancies can modify risk of disease evolution (such as Vitamin C for those with TET2 lesions) has not yet been determined.8 Prospective studies that track clone size, molecular evolution, and clinical outcomes will require large numbers of patients followed over long periods. Early intervention studies might instead focus on patients with the highest risk (like Jeannie) who carry a predisposition allele, CCUS patients, or individuals with CHIP after cytotoxic therapy.

Ultimately, we will need to develop approaches to attack the highest risk clones before they attack us.


Rafael Bejar is on the Data Monitoring Board, the Steering Committee, and the ad hoc Advisory Board for Celgene. He receives research funding from Takeda and is a consultant for Genoptix. Dr. Sekeres is on the Advisory Boards and Steering Committees for Celgene, Millennium, and Syros.
IN MEMORIAM

Quintessential Collegiality
Evans Sadler MD, PhD (1951 - 2018)

J. Evan Sadler III, MD, PhD, the Lang Professor of Medicine and Chief of Hematology at Washington University in St. Louis, passed away on December 13, 2018, after a brief but devastating illness. Evan was 67 years young, an outstanding academic hematologist, and a great citizen of science and life.

Evan was born in West Virginia and showed incredible intellectual promise and curiosity from a young age. That promise led Evan to Princeton, where he graduated Summa Cum Laude and Phi Beta Kappa, majoring in chemistry. Evan then entered the MD/PhD program at Duke University where he trained with Bob Hill in enzymology and protein biochemistry, as Evan put it years later, disciplines fundamental to learning how molecules worked. This was a productive time for Evan, both scientifically and romantically, as he met Linda Pike, a PhD student in Bob Lekowitz’s laboratory, forming an incredible couple, ultimately giving rise to what Evan referred to as “the three musketeers” — Brooke and Evan D.

Following his MD/PhD training, Evan remained at Duke for his internal medicine residency, followed by a hematology fellowship at the University of Washington in Seattle, training in the laboratory of Earl Davie. For those of us who were trained with and aware of Evan in his early career, it was clear that he was an incredibly intelligent, precise, and inquisitive scientist, and a serious student of all things scientific. During a visit to the Galapagos Islands, Evan’s prior encounter with a very old tortoise, which as a tortoise had also been gazed upon by a twentysomething scientist named Charles Darwin, turned the trip into his “best ever”.

As a clinical hematologist Evan was intrigued by normal and disordered blood coagulation, so what better research fellowship project for him than cloning the gene for the “factor” responsible for von Willebrand Disease (VWD)? Evan’s successful cloning of von Willebrand Factor (VWF) launched his scientific pathway to hundreds of publications and millions of dollars in sponsored research.

Evan’s early successes led to a Howard Hughes Medical Institute investigatorship, which he held for more than 25 years, and an appointment at Washington University, where he remained on faculty for his entire academic career. During this time, Evan had a profound effect on the field of blood coagulation and its disorders. He was a key thought leader in defining the complexity biology and genetics of VWD, and establishing the current criteria for its diagnosis. Evan deciphered the biochemical pathways responsible for the assembly of the 300 kDa VWF monomer into huge, ultrahigh molecular weight molecules that measure microns in length. Along with others, Evan’s work on ADAMTS13, the protease that cleaves ultrahigh molecular weight VWF to the size found in normal plasma, unraveled the molecular basis for congenital and acquired thrombotic thrombocytopenic purpura. The impact of his scientific contributions was recognized by his election to numerous honorific scientific societies, including the American Society for Clinical Investigation, the Association of American Physicians and the National Academy of Medicine, and garnered him multiple awards from the American Society of Hematology and the International Society for Thrombosis and Hemostasis.

But beyond his scientific impact, Evan Sadler embodied integrity and collegiality, setting the tone for our entire field. It never mattered to Evan who did something first or got the credit — what really mattered was solving the scientific problem at hand in the most rigorous fashion. He was a caring mentor to over 50 trainees in his own lab as well as innumerable trainees and junior faculty members at his own and other institutions. Evan gave back to his professional societies, serving on numerous editorial boards and as an elected officer including President of ASH; he also organized a large number of scientific meetings and conferences. Evan was a student of all life, equally comfortable speaking about diverse topics from protein biochemistry to French cooking, or the ethics of Aristotle. He was a devoted father and husband, a ballroom dancer and a runner, and a treasured friend and colleague to so many.

Because of his viceroy for life, this remembrance of Evan Sadler requires one last story. Wherever Evan traveled, he brought along his running shoes and his stopwatch. One of us (KK) ran with Evan wherever we were together, in Bethesda, Bermuda, New Orleans, New Hampshire, and all around the world. The same drive for precision that led to Evan’s scientific successes carried over to running. Evan kept the precise duration of our runs, including stopping his stopwatch when we came to a red light, starting it up again only when the light turned green. Seriously. But perhaps the most remarkable example of his drive for precision came when a run in Philadelphia was punctuated by a bout of a heart rhythm disturbance, supraventricular tachycardia (SVT). Because the abnormal rhythm was distressing and reduced his exercise capacity, whenever Evan developed SVT during a run, he stopped, then stopped the stopwatch, performed cardiot sinus massage to stop the SVT, before starting the run, and the stopwatch, again. Precision embodied.

Evan Sadler was a scientific and clinical giant in the field of hemostasis, whose contributions to biomedical research and to patient care will live long after him.

With great fondness and respect,
Kenneth Kaushansky, MD, and David Ginsburg, MD

ASH Member Speaks to the Grassroots Network About Running for Congress

At the ASH Grassroots Network Lunch during the 2018 ASH Annual Meeting in San Diego, Dr. Jason Westin shared his story of running for office in Texas’s seventh congressional district. In 2018, Dr. Westin, an ASH member, encouraged other hematologists to be advocates for their patients and science. “I think the folks who are in power right now would benefit from having more people such as hematologists … get more involved,” said Dr. Westin.

In an interview with ASH News TV following the lunch, Dr. Westin noted that there are many ways for hematologists to advocate for issues affecting research and practice as well as their patients, ranging from educating legislators to running for office. “We get tunnel vision in what we do in terms of science and in terms of clinical trials and research, and we don’t often appreciate the expertise that we have and that the public gives us credence for,” he said. “I think our expertise is not utilized to its full potential if we’re sitting on the sidelines.”

Also, during the lunch session, Chair of the ASH Committee on Government Affairs Dr. Alan Rosmarin highlighted many of ASH’s recent advocacy efforts. In 2018, the Grassroots Network conducted more than 1300 computer simulations of the Affordable Care Act (ACA) for patients with sickle cell disease. The Grassroots Network also successfully advocated for the Sickle Cell Disease and Other Heritable Blood Disorders Research, Surveillance, Prevention, and Treatment Act (S. 2465) which passed both chambers of Congress and was sent to the President for his signature in December. The new law authorizes sickle cell disease (SCD) prevention and treatment grants awarded by the Health Resources and Services Administration and authorizes the federal government to award data collection grants via the Centers for Disease Control and Prevention

Further highlights from 2018 saw Grassroots Network members working to raise public health funding levels, ensuring patients have access to quality care, and supporting physician payment. But as we look to 2019, ASH members also spent time educating legislators and their staff by participating in multiple ASH-organized congressional briefings on SCD and chimeric antigen receptor therapy (CAR T).

This year, and throughout the new 116th Congress, ASH will continue its advocacy efforts on several important research and practice-related issues including seeking increased federal funding for research, responding to changes in physician reimbursement, ensuring access to safe and effective hematologic drugs, and supporting legislative initiatives concerning sickle cell disease treatment and research.

The Society needs the help of all ASH members to bring issues important to the future of hematology to the attention of the U.S. Congress including the many new members in both the House of Representatives and Senate as well as the administration and U.S. governmental agencies. Members of the ASH Grassroots Network receive action alerts and information about issues of interest. At times, Grassroots Network members are also invited to represent hematology in activities such as visits to Capitol Hill, meetings with NIH leadership and other regulatory agencies, and in visits with congressional leaders back home. Visit the ASH Advocacy Center at www.hematology.org/advocacy to participate in the Society’s advocacy campaigns and to join the ASH Grassroots Network. To read about ASH’s policy and advocacy efforts, visit www.hematology.org/Advocacy/PolicyNews.aspx.

Apply for the ASH Congressional Fellowship by January 31

ASH is accepting applications for the 2019 ASH Congressional Fellowship. This yearlong opportunity beginning in September 2019 will place a hematologist who is an ASH member on Capitol Hill to work in a Congressional office and help shape health care and hematology policy. The fellowship aims to provide education about the policy-making process including Congress’ relationship to the hematology community and provides an opportunity to educate Congressional members and staff about hematology. For requirement, meet additional information, or to apply by the deadline of January 31, 2019, visit www.hematology.org/ CongressionalFellowship.
Blood to underscore the remarkable research that is published in some of the most outstanding articles that have appeared either in print or online during the two-month interval between issues of The Hematologist. The goal is to underscore the remarkable research that is published in Blood and to highlight the exciting progress that is being made in the field.

D E C E M B E R  2 7 ,  2 0 1 8

In a plenary paper, Dr. Sebastien Jacquelin and colleagues report that Dnmt3a deletion in Jak2V617F murine hematopoietic stem cells followed by transplantation into lethally irradiated mice gives rise to a rapidly progressive myelofibrosis.


Dr. Lorenz Thurner and colleagues demonstrate that eight of 12 samples from patients with primary central nervous system lymphoma (PCNSL) had B-cell receptors recognizing hyperglycosylated CNS-restricted proteins SAMD-14 and neurabin-I. These studies provide pathophysiologic insight into the drivers of the disease and its tropism for the CNS. They further offer a potential target for future therapy.

J A N U A R Y  3 ,  2 0 1 9

In this plenary paper, Dr. Courtney D. DiNardo and colleagues present early-clinical-phase data on the safety and efficacy of the BCL-2 inhibitor venetoclax combined with hypomethylating agents for remission induction in older individuals with acute myeloid leukemia.


The investigators present a novel therapeutic strategy for chronic graft-versus-host disease (cGVHD) and demonstrate that a small-molecule inhibitor is able to reverse lung injury due to experimental cGVHD by targeting B-cell lymphoma 6 (BCL6), a transcriptional regulator of T follicular helper cells and germinal center B cells.


This study presents thorough experimental evidence demonstrating that targeted therapy with the combination of PI3Kα/δ inhibition (copanlisib) and BCL-2 blockade (venetoclax) is synergistic in B-cell receptor–dependent diffuse large B-cell lymphomas (DLBCL) with molecular features of BCL-2 dysregulation.

J A N U A R Y  1 7 ,  2 0 1 9

This plenary paper links bleeding in cerebral cavernous malformations, which are common brain vascular defects, to anticoagulant activity of local endothelial cells, and it explores novel ways to reduce accompanying seizures and strokes.


The data in this paper reveal critical roles of cholinergic pathways in circadian regulation of hematopoietic stem cell–trafficking dynamics.


This study demonstrates that sickle cell disease (SCD) disrupts an entirely new pathogenic pathway that may be targeted to treat the disease. These data provide compelling evidence that there is a defect in the inflammation-resolution response in the humanized model for SCD and that its restoration with the addition of 17R-resolvin D1 prevents tissue injury.


The authors report thioredoxin-related transmembrane protein 1 (TMX1) as the first antithrombotic vascular thiol isomerase. The intrinsic platelet membrane oxidoreductase TMX1, the fifth member of the protein disulfide isomerase family of enzymes, is required for normal platelet function and thrombosis in mice.
Much-Needed Progress in Therapies for Myelodysplastic Syndromes

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This time last year, we reviewed the remarkable news of several new U.S. Food and Drug Administration (FDA)-approved therapies for acute myeloid leukemia (AML).1 After decades without new treatments, in 2017 four new drugs were approved for patients with AML; these include incleromide, vynxere, enasidenib, and gemtuzumab ozogamicin. At the beginning of 2018, vosudarin was approved for relapsed/refractory AML with BRCM mutations followed by the exciting approvals of venetoclax in combination with azacitidine, decitabine, or low-dose cytarabine as initial therapy for newly diagnosed AML in adults older than 75 years. Now it seems that the therapeutic landscape may also be improving for myelodysplastic syndromes (MDS). Several advances in novel and targeted therapies for MDS were highlighted at the 2018 ASH Annual Meeting.

The last FDA approval of a drug for MDS occurred in 2006 with the approval of lenalidomide for low- or intermediate-risk MDS with 5q deletion. Before that, azacitidine and decitabine were approved in 2004 and 2005, respectively. While these drugs were surely breakthroughs and have helped extend and improve the lives of numerous MDS patients, they are not curative for most and relapsed disease is almost certain. The only known cure for MDS is an allogeneic hematopoietic stem cell transplant, the use of which can be limited by the older age and attendant comorbidities of typical MDS patients. Therefore, the need for new therapies is great for newly diagnosed and relapsed/refractory patients, as well as patients that relapse after transplant.

For many years our understanding of MDS was derived from research in AML due to the lack of cell lines and preclinical in vivo models of MDS. That has changed somewhat over the last decade as studies of the genetics of MDS have been performed on microenvironment, genetically engineered mouse models, and humanized mouse xenografts have shed light on the genetics and biology of MDS. One important finding from this effort was the discovery that TGF-β signaling contributes to the erythroid maturation defect in MDS and that decreased TGF-β signaling achieved through a TGF-β receptor inhibitor (ACE-536, luspatercept) can restore normal erythroid maturation.2 The therapeutic relevance of this finding was reported in the phase 3 trial at the 2018 ASH Annual Meeting in the form of a phase 3, randomized, double-blind, placebo-controlled study. In this trial, luspatercept resulted in a significantly reduced transfusion burden in patients with anemia due to very low, low, or intermediate-risk MDS with ring sideroblasts (MDS-RS).

MDS-RS has a unique association with mutations in the splicing factor, SFPB13; however, this only accounts for a subset of MDS bearing mutations in splicing proteins including SF3B1, SRSF2, LMX1b, or HOXB4. Moreover, more than 50 percent of patients with MDS have mutations in one of these splicing factor genes.4 While the exact pathogenic role these mutations play in MDS biology is still being worked out, it’s clear that cell lines and patient-derived xenografts bearing splicing factor mutations are more sensitive to spicosomal disruption than wild-type cells in preclinical assays.5 This hypothesis is being further tested clinically in a phase 1 trial of a novel spicosomal modulator named H3B-8800 (NCT02841540) in relapsed/refractory myeloid malignancies with splicing factor mutations including MDS and chronic myelomonocytic leukemia.

Other MDS clinical advances highlighted at the 2018 ASH Annual Meeting are the novel hypomethylating agent guadecitabine, eltrombopag, and the nuclear export inhibitor selinexor. The investigator-initiated phase II trial of selinexor (NCT02228525) found an overall response rate of 32 percent in high-risk patients refractory to hypomethylating agents, a very tough group to treat. Selinexor inhibits the function of the main nuclear protein exporter, XPO1, and thus interferes with many important cellular processes. Discovering why only a subset of patients respond is of extreme interest as many of these patients may help us learn which of the downstream effects of selinexor is the most important for response. This information might lead to a biomarker that would allow for targeted application of selinexor to a group enriched for responses.

There are other exciting therapies on the horizon for MDS including IDH1/2 inhibitors, pemovastinat (a NEDD8-activated enzyme inhibitor), and glasdegib (a smoothened inhibitor that targets the Hedgehog pathway and was just approved by the FDA for AML). While a phase 2, randomized controlled trial in children and adults with sickle cell disease (SCD).6 In a double-blind randomized controlled trial in children and adults with SCD, when compared to placebo, oral L-glutamine therapy taken twice daily for approximately a year was associated with decreased incidence rate of acute vaso-occlusive events.

The FDA approval of L-glutamine, only the second approved drug for sickle cell disease (SCD) in more than 20 years, has both symbolic and clinical importance. Conceptually, individualized care with SCD and the hematologist has been central to the care of patients participating in clinical trials sponsored by the National Institutes of Health (NIH), foundations, and industry, they have not been forgotten. The FDA’s recent approval provides tangible evidence that while SCD is actively working to ameliorate intolerable acute painful episodes — the hallmark of the disease.

Scientifically, the results of the trial provide mounting evidence that novel therapies, other than those targeted at increasing levels of fetal hemoglobin, may decrease the severity of the disease. The primary basis for the trial is that red blood cells (RBCs) in individuals with SCD have increased concentrations of reactive oxygen species compared with normal RBCs. Consequently, glutathione levels are depleted within RBCs of individuals with SCD. Key substrates (cysteine, glutamate, glutamine, and glycine) of the glutathione cycle are increased. Prior research indicated that oral L-glutamine can significantly increase the NAD redox potential and NADH level in sickled RBCs, which led to a phase III trial of 238 individuals with SCD that were randomly allocated to 0.6 mg/kg daily of L-glutamine or placebo for six months.7 The preliminary results were very promising and demonstrated a significant decrease in the incidence of vaso-occlusive events (3 vs. 4, p=0.005) and hospital days (6.5 vs. 11, p=0.0045) with no increase in adverse events when compared to placebo. Ultimately, Dr. Nihara and colleagues designed and successfully completed the phase III trial.

In the past year, multiple SCD trials have targeted anti-inflammatory therapies for the prevention of acute vaso-occlusive episodes. Crizanlizumab, a humanized, α4β1 integrin monoclonal antibody, was the therapeutic agent used in a randomized, double-blind, phase II, controlled trial, referred to as the Sustain Study.8 α4β1 selectin, a cell adherence molecule expressed in sickled RBCs, endothelial cells, white blood cells, and activated platelets was the biological basis for the novel therapy. In the phase II trial, the investigators demonstrated that crizanlizumab at 5 mg/kg, 14 times during 52 weeks, when compared to placebo, significantly decreased incidence rates of vaso-occlusive pain episodes (1.63 vs. 2.98; p=0.01), and significantly delayed the median time to first vaso-occlusive pain episode (4.07 vs. 1.38 months; p=0.001). In a follow-up subgroup analysis of the same phase II trial, the investigators demonstrated that regardless of the number of acute vaso-occlusive pain events in the year prior to entering the trial, treatment with 5 mg/kg of crizanlizumab when compared to placebo was associated with a statistically significant lower hazard ratio of time to first vaso-occlusive event.9

In a 2018 phase II trial, Dr. Jeffrey Glassberg and colleagues demonstrated that in adults with SCD without asthma, once-daily mometansone furoate 220 μg dry powder inhalation, when compared to placebo throughout 16 weeks, had a higher reduction in daily pain score of 1.42 points (95% CI, 0.61−2.21; p=0.001).10 Collectively, the promising results of both phase II trials demonstrate that anti-inflammatory strategies could provide unique opportunities for combination therapy to decrease the incidence rate of acute vaso-occlusive events in children and adults with SCD.

The new phase II and phase III trials, the National Heart, Lung, and Blood-led Cure Sickle Cell Initiative, the development, the ASH Research Collaborative’s clinical trials network, the open investigator-initiated and industry-sponsored gene therapy trials, and the two ongoing NIH-sponsored hematopoietic stem cell transplantation trials make the future look bright for patients with SCD. As we look to future FDA-approved therapies for treating SCD symptoms, each one bringing us close to a day when the disease may routinely and safely be cured.


Dr. Taylor and Dr. Abdel-Wahab indicated no relevant conflicts of interest.
In Search of Missed Tumors: Next-Generation Sequencing for Minimal Residual Disease Detection in Multiple Myeloma Comes of Age

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Multiple myeloma (MM) is an incurable plasma cell malignancy that resides in the bone marrow. Despite significant advances in treatment and prognosis, most patients eventually relapse, presumably because of undetected residual disease. Earlier detection of MRD is of utmost importance, given that the bone marrow biopsy, does not preclude relapse or death. Instead, a molecular or immunophenotypic CR that identifies residual tumor at increased depth, compared to standard clinical assessment, is a better predictor of disease outcome. Naturally, the accuracy of those predictions is a function of technological limitations and assay design, and to some degree, spatial heterogeneity and stochastic sampling. The principle, however, is quite simple: The more sensitive the method, the more reliable the predictions.

Minimal residual disease (MRD) in MM is currently assessed by multicolor flow cytometry, allele-specific oligonucleotide polymerase chain reaction (ASO-PCR), and next-generation sequencing (NGS) of bone marrow samples. Eight-color flow cytometry and ASO-PCR both have a sensitivity of $10^{-4}$ (allowing for detection of one tumor cell in a background of 100,000 normal cells), and are used as predictors of progression-free survival (PFS) and overall survival (OS). On the other hand, clonotype analysis by VDJ sequencing has an increased sensitivity of $10^{-6}$, allowing for more accurate measurement of residual disease.$^{10}$ However, significant optimization, so-called next-generation eight-color flow cytometry (NGF) achieved comparable sensitivity. $^{11}$

NGS has significantly improved our understanding of cancer biology and informed cancer taxonomy, prognosis, and treatment. Moreover, as sequencing costs have dropped dramatically, NGS is now also increasingly used as a clinical detection tool.$^{12,13}$ Examples of this include the Dana-Farber Cancer Institute’s (DFCI) targeted NGS assay, OncoPanel, and the U.S. Food and Drug Administration (FDA)–approved Memorial Sloan Kettering–Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT).$^{14}$ Although capture-based deep targeted sequencing assays like this can be useful for the precise quantification of vector-derived therapeutic globin expression, these approaches are limited in their ability to detect clonotypically distinct MRD variants that are present at low levels (less than 1 in 10,000) and have been shown to be associated with relapse in patients undergoing immunotherapy for melanoma. $^{15}$

The recently FDA-approved clonoSEQ assay takes advantage of the uniform presence of single VDJ rearrangements across all cells of an individual tumor to detect MRD in patients with MM.$^{16}$ More specifically, the IgH locus of diagnostic samples is amplified in a multiplex fashion using consensus primers followed by targeted sequencing and clonotype calling; the clonotype can then be tracked by clonoSEQ. Although the method is simple in its perception, IgH locus amplification through multiplex PCR represents a practical challenge due to significant sequence homology in the region and variable primer specificity and kinetics. To address that issue, clonoSEQ uses proprietary chemistry based on a synthetic receptor library which allowed for experimental and computational optimization of the multiplex PCR assay.$^{17}$ These technological advances led to a sensitivity lower than 10^{-6} which made clonoSEQ an important tool for MRD detection in B-cell malignancies including MM.$^{18,19}$ Sensitive MRD detection is likely to not only provide better survival estimates for patients with MRD but also redefine the risk factor landscape in MM and help distinguish variables that truly reflect aggressive biology.

A recent study by Dr. Aurore Perrot and colleagues in patients from the Intergroupe Francophone Du Myelome (IFM)-DFCI cohort confirmed that MRD negativity, as assessed by clonoSEQ, is a major prognostic factor in MM.$^{20}$ Notably, despite a significantly higher rate of MRD negativity in patients who underwent transplantation, compared to those who were treated with TCV (lenalidomide, bortezomib, dexamethasone) alone, MRD-negative patients had similar outcomes (PFS/OS) irrespective of treatment arm.$^{21}$ Additionally, patient outcome was independent of cytogenetics and International Staging System (ISS) stage.$^{22}$ These results seem to suggest that in patients who achieve MRD negativity by clonoSEQ, the MRD status by clonoSEQ, the effect of transplantation as well as the prognostic significance of cytogenetics and ISS stage, have which have long been considered important outcome predictors,9,10 should be re-evaluated. It should be mentioned though that statistical significance is largely a function of sample and effect size and there is a clear trend in favor of transplantation, standard-risk cytogenetics, and ISS Stage I, even in patients who achieved MRD negativity by clone-Seq.$^{23}$ In fact, LMCAR (26.1%) was not achieved in 14% of patients.$^{24}$

Despite its increased sensitivity, clonoSEQ can still miss residual tumor in patients.$^{11,12}$ Those who achieve MDR negative status by means of VDJ targeted sequencing can still relapse, leaving significant room for improvement of MRD detection methods. Nevertheless, MRD negativity detected by NGS in MM is now confirmed to be strongly prognostic for PFS and OS. Its gradual incorporation into clinical trial design and clinical practice is poised to change MM patient management as we know it.


Romanos Sklavenitis-Pistofidis and Dr. Dong indicated no relevant conflicts of interest.

Irene Ghobrial is on the Advisory Board of Celgene, Takeda, Janssen, BMS, and Sanofi.

The @hematologist ASH NEWS and REPORTS

Lentiglobin Gene Therapy Looks Promising in Patients With Transfusion-Dependent β-thalassemia

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The β-hemoglobinopathies, beta-thalassemia (β-thalassemia) and sickle cell disease (SCD), are the most common monogenic diseases worldwide and constitute a growing and major burden on health services in many nations. These disorders result from mutations in the β-globin gene locus that lead to the production of abnormal (β*) or abnormal (δβ) globin protein. In β-thalassemia, reduced β-globin production leads to an imbalance in the ratio of α to β chains leading to ineffective erythropoiesis, chronic hemolysis, and profound anemia. Bone marrow transplantation is the best well-characterized curative treatment, but new therapies have improved their prognosis, patients with transfusion-dependent β-thalassemia continue to suffer organ damage due to iron overload and other complications of their disease. Allogenic hematopoietic stem cell transplantation, while curative, confers significant risks of morbidity and mortality and is limited by donor availability. Gene transfer achieved by transplantation of the patient’s own stem cells that have been genetically-modified with a corrected gene offers a potential alternative curative therapy. The first proof of principle of its therapeutic benefit was reported a decade ago utilizing a β-globin expressing lentivirus in a patient with transfusion-dependent thalassemia (β*β*). In 2018, that excitement advanced in this field.

Dr. Alex Thompson and colleagues reported interim results of two early-phase clinical studies (HGB-204 and HGB-205) evaluating the safety and efficacy of gene therapy for β-thalassemia using a lentiviral vector (Lentiglobin BB305) encoding β-globin engineered with a single amino acid substitution (T9Q). This amino acid change strongly inhibits the polymerization of sickle hemoglobin in patients with SCD and also allows polymerization to be reactivated by vector-derived therapeutic globin expression in vivo. Twenty-two patients with transfusion-dependent β-thalassemia (12-35 years of age) underwent myeloablative busulfan conditioning followed by infusion of autologous CD34+ stem/progenitor cells transduced ex vivo with a lentiviral vector. Follow up after transplantation...
Transfusion-dependent \(\beta\)-thalassemia is a severe genetic disease. Gene therapy offers a potentially transformative option for these patients. Phase III trials are now underway and should help to determine the benefit, risks, and cost/benefit analysis of this approach.


CAR-T Tcomes to the Rescue: Cell Therapy Makes 2018 Headlines in the Management of Relapsed Large B Cell Lymphoma

By Dr. Keel indicated no relevant conflicts of interest.


As lymphoma subtype, germinal center B-cell and activated B-cell DLBCL, refractory subgroups, low and high International Prognostic Index (IPI), and bulky or extranodal disease. It almost seems that if T cells can be appropriately expanded and maintained in vivo, they will kill B-cell tumors irrespective of phenotype, genetics, or tumour bulk.

The currently positioning of therapy in the management of large B-cell diffuse lymphoma is in patients who have failed initial therapy and do not achieve a good response to successful salvage chemotherapy and subsequently autograft. Dr. Victor A. Chow and colleagues have suggested how cell therapy may fit into the 2018 algorithm of DLBCL therapy although some of these decision points currently need further evidence (Figure E1). This is already a large group of patients and will bring CAR-T therapy into the therapeutic armamentarium of most hematologists. The potential implications for clinical delivery are profound and if many centers are unable to administer such products, it may centralize delivery of care.

Of course, there are considerable toxicities with CAR-T. The two major acute toxicities are cytokine release syndrome (CRS) and neurotoxicity. These are now managed according to standardized regimens and although grade 3+ CRS and neurotoxicity adverse events were seen in 13 percent and 31 percent of patients respectively in ZUMA-1, these are typically reversible.

The profile of clinical response for CAR-T therapy of relapsed large B-cell lymphoma that emerges at the end of 2018 consists of a sustained CR of 30 to 40 percent. When compared to the median survival of just six months in the retrospective SCHOLAR-1 study, the results are stunning but still leave 60 percent of patients with a poor outcome. Treatment failures can relate to inadequate expansion of the infused product, loss of CD19 on the tumour cell, or local immune suppression such as increased PD-L1 expression. Huge research programs are currently addressing all three of these challenges.

So, how do we proceed with CAR-T in large cell lymphoma? Phase III randomized trials are needed to directly compare the efficacy of CAR-T therapy with high-dose chemotherapy and autologous transplantation after first relapse. At some point, they will enter first-line therapy for patients with high-risk features. Inevitably they are also being assessed in the indolent lymphomas. A year may seem like a long time in hematology, but progress in CAR-T biology and therapy works to a much shorter timeframe.

Hematologists may be consulted on patients with unexplained arterial thromboembolism, such as stroke, heart attack, and renal, mesenteric, or central retinal artery thrombosis, both to help clarify the etiology of the thromboembolic event and give input into the best management choice (i.e., the decision as to whether anticoagulant or antiplatelet therapy is the preferred treatment option). A systematic approach to such patients is helpful so that all possible causes of arterial thrombosis are considered and the hematologist’s focus is not simply on testing for thrombophilia (Table).

While limited data exist on best treatment of unexplained arterial thromboembolic events in several of these anatomic territories, data have shown that in patients with ischemic stroke of uncertain cause, also termed “cryptogenic” or “noncardiogenic” stroke, anticoagulation with warfarin was not superior to antithrombotic prophylaxis with aspirin in secondary stroke prevention and led to an increased risk for bleeding. Based on these findings, aspirin traditionally has been used for secondary stroke prevention in noncardiogenic stroke. In 2014, a new term, "Embolic Stroke of Undetermined Source" (ESUS), was coined for a subgroup within the cryptogenic stroke category. ESUS is defined by four criteria: (1) a nonlacunar brain infarct on imaging, (2) patent arteries (< 50% stenosis) proximal to the infarct, (3) absence of major-risk cardioembolic source, and (4) no other specific cause of stroke identified. Potential causes of ESUS include undetected paroxysmal atrial fibrillation or other arrhythmia, structural heart disease, arteriogenic embolism, and/or paradoxical emboli from venous circulation, all of which may not be identified with standard diagnostic assessment. The identification of ESUS as a clinical entity has possible important treatment implications. There is long-standing evidence that in ischemic stroke from a proven embolic source, secondary stroke prevention with anticoagulation is superior to antiplatelet therapy. Therefore, designating a stroke as ESUS rather than cryptogenic, it suggests that the patient should be placed on anticoagulation.

In the New England Journal of Medicine in June 2018, the NAVIGATE ESUS Investigators presented results from an international, randomized, phase III trial comparing rivaroxaban 15 mg once daily with aspirin 100 mg daily for secondary stroke prevention in patients with previous ESUS as defined by Dr. Robert G. Hart and colleagues. After a second interim analysis, approximately three years after initiation of enrollment and after enrollment of 7,213 patients (3,605 in the rivaroxaban arm and 3,604 in the aspirin arm), the trial was terminated because rivaroxaban did not lead to a lower rate of thromboembolism compared with aspirin, yet increased the risk of bleeding. The primary efficacy outcome (recurrent stroke or systemic embolism) occurred at similar rates in both groups, resulting in 5.1 percent per year in the rivaroxaban group compared to 4.8 percent per year in the aspirin group (HR, 1.07; 95% CI, 0.87-1.33; p=0.52). The overwhelming majority of events were ischemic strokes (95%), with similar stroke severity in each group. Major bleeding occurred at a rate of 1.8 percent per year in the rivaroxaban group, compared with 0.7 percent per year in the aspirin group (HR, 2.72; 95% CI, 1.68-4.39; p=0.001). There was also an increased rate of life-threatening or fatal bleeding in the rivaroxaban group compared with the aspirin group (1.8% vs. 0.4% per year; HR, 2.34; 95% CI, 1.28-4.29; p=0.004). An increase of clinically relevant nonmajor bleeding (3.5% vs. 2.3% per year; HR, 1.51; 95% CI, 1.13-2.00; p=0.004) and an increase of symptomatic intracranial hemorrhage (0.6% vs. 0.1% per year; HR, 4.02; 95% CI, 1.51-10.7; p=0.003).

A potential limitation of the study is the inclusion criteria used to designate ESUS. A commentary on the publication of Dr. Hart and colleagues highlighted that arteriosclerotic plaques, even when less than 50 percent of artery diameter, can rupture with resultant arterial occlusion that is best prevented with antiplatelet therapy. Perhaps with more stringent arteriosclerotic criteria, the study population would have been more heavily weighted toward embolic sources, and thus, may have had shown benefit with anticoagulation. However, this theory has not yet been investigated.

While limited data exist on best treatment of unexplained arterial thromboembolic events in several of these anatomic territories, data have shown that in patients with ischemic stroke of uncertain cause, also termed “cryptogenic” or “noncardiogenic” stroke, anticoagulation with warfarin was not superior to antithrombotic prophylaxis with aspirin in secondary stroke prevention and led to an increased risk for bleeding. Rather than anticoagulant therapy is currently the treatment standard for patients with ESUS.

### A. Is arteriosclerosis the underlying problem?
- Arteriosclerotic changes demonstrated on imaging studies (ICT, contrast angiography, Doppler ultrasound) or on pathology specimens?
- Arteriosclerosis risk factors present?
- Cigarette smoking
- Hypertension
- High low-density lipoprotein cholesterol
- Low high-density lipoprotein cholesterol
- High lipoprotein(a)
- Diabetes mellitus
- Obesity
- Family history of arterial disease in young relatives (age < 50 years)

### B. Has the heart been evaluated as an embolic source?
- Atrial fibrillation – EKG, Holter, or event monitor
- Patent foramen ovale – cardiac echo with bubble study and Valsalva maneuver

### C. Other causes
- Is the patient on estrogen therapy (contraceptive pill, ring, or patch; hormone replacement therapy)?
- Does the patient use cocaine or anabolic steroids?
- Is there evidence for Buerger’s disease (does patient smoke or use tobacco)?
- Does patient have symptoms suggestive of a vasoplastic disorder (Raynaud’s disease)?
- Were anatomic abnormalities seen in artery leading to the ischemic area (web, fibromuscular dysplasia, dissection, vasculitis, or external compression)?
- Does patient have evidence of a rheumatologic or autoimmune disease (arthritis, purpura, or vasculitis)? Consider laboratory work-up for vasculitis and immune disorder?
- Is there a suggestion of an infectious arteritis?
- Could the patient have hypercoagulability?

### D. Thrombophilia work-up considerations
- Hemoglobin and platelet count*
- Antiphospholipid antibodies
- Anticardiolipin IgG and IgM antibodies
- Anti-β2-glycoprotein-I IgG and IgM antibodies
- Lupus anticoagulant
- Protein C activity
- Protein S activity and free protein S antigen
- Antithrombin activity
- Homocysteine
- Factor V Leiden and prothrombin 20210 mutation (purpose of testing: to detect the homozygous or double heterozygous state)

*In case of complete blood count abnormalities, consider paroxysmal nocturnal hemoglobinuria and/or myeloproliferative neoplasm testing. Note: Do not test for methylene tetrahydrofolate reductase polymorphisms, PAI-1, or tPA levels or polymorphisms, fibrinogen, or factor VIII activities.
Rivaroxaban Clinical Trials in 2018: Successes, Failures, and Lessons Learned

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2018 was a banner year for rivaroxaban clinical trials, with the results of COMPASS,3 COMMANDER HF,4 NAVIGATE ESUS,5 MARINER,6 and SELECT-D7 announced. The first three studies were designed to reduce arterial events, while the latter targeted venous thromboembolism (VTE). In total, more than 28,000 study participants were exposed to rivaroxaban in doses ranging from 2.5 mg twice daily (bid) to 15 mg bid. The goal of this review is to briefly summarize the trial results and attempt to put them into context (Table). Categorization of a study as a “success” or “failure” is based solely on achievement of the study’s primary outcome.

Arterial Endpoints

Success – COMPASS: This trial showed that for patients 65 years or older with stable coronary disease or peripheral artery disease, very-low-dose rivaroxaban (2.5 mg bid) plus aspirin (100 mg once daily [od]) reduced the risk of the composite outcome of myocardial infarction, stroke, or cardiovascular death (HR, 0.74; 95% CI, 0.65-0.86; p<0.001).1 Similarly, in the peripheral artery disease subgroup, the prespecified outcome of major adverse limb events was reduced by nearly half in the very-low-dose rivaroxaban plus aspirin arm (HR, 0.54; 95% CI, 0.35-0.82).2

Not surprisingly, the risk of bleeding was increased in both rivaroxaban arms compared to aspirin alone despite a 30-day run-in phase with aspirin, likely selecting out the patients at highest risk for bleeding. It is also worth noting that the trial was terminated early for efficacy which has raised concern that the bleeding rates are underestimated.

Failure – COMMANDER HF and NAVIGATE ESUS: The COMMANDER HF trial showed that the same dose of rivaroxaban that was successful in COMPASS (2.5 mg bid) did not prevent the composite primary outcome of all-cause death, myocardial infarction, or stroke in patients with recent coronary revascularization (n=24,824).3

In NAVIGATE ESUS, rivaroxaban 15 mg od did not reduce the risk of first recurrent stroke in patients with recently exacerbated chronic heart failure compared with standard care alone.4 Single or dual antiplatelet therapy were allowed in both arms (98% of study participants were taking at least one antiplatelet agent at baseline).

Venous Endpoints

Success – SELECT-D: This trial showed that rivaroxaban was noninferior to low-molecular-weight heparin for treatment of patients with cancer-associated thrombosis.5 SELECT-D was powered as a pilot study, which limits conclusions. However, this result together with the results of the HORIZONS trials6 are slowly shifting the treatment of selected cancer patients toward direct oral anticoagulants (DOACs).

Failure – MARINER: This trial showed that rivaroxaban 10 mg daily for 45 days after discharge for medical patients 40 years or older did not reduce the composite of symptomatic VTE or fatal bleeding death compared to placebo.6 Interestingly, this result occurred despite the use of a high IMPROVE score and elevated D-dimer as enrollment criteria in an attempt to target patients at higher baseline risk for VTE. The overall event rate was very low, and similar to the arterial trials, the risk of major bleeding was increased in the rivaroxaban arm.

Lessons Learned

The first lesson learned by these trials is one we already knew: Anticoagulant therapy reduces thrombotic events, but excessive bleeding can completely overshadow this benefit. This is the primary reason why older trials using warfarin following ischemic stroke7,8 or cancer combined with aspirin for secondary prevention of cardiovascular events failed. COMPASS was able to tip the scales in favor of benefit because it used a very low dose of rivaroxaban. In contrast, the reduction of symptomatic thromboembolism provided by low-dose rivaroxaban in MARINER was not enough to compensate for bleeding, despite the attempt to enroll a study population at higher risk for VTE.

The next lesson learned is the target must be right. COMMANDER HF and NAVIGATE ESUS showed that while thrombin generation may contribute to adverse events in these study populations, it is unlikely to be the primary mechanism. Ongoing trials with other DOACs in similar patient groups should support or refute this hypothesis.9,10

Lastly, anticoagulant therapy is not one-size-fits-all. For example, for secondary prevention of cardiovascular events, very-low-dose rivaroxaban (combined with aspirin) seems to be the correct dose, but 20 mg is needed to prevent stroke secondary to atrial fibrillation (15 mg if creatinine clearance is 30-49 mL/min).11 With additional doses now entering the market, there is a real danger of clinicians ordering the wrong dose for a given indication. Clinicians tend to order lower doses thinking (correctly) they can carry a lower risk of bleeding. However, depending on the patient population, the efficacy will also be substantially reduced if the wrong dose is selected.

Summary of Large Rivaroxaban Clinical Trials Reported on in 2018

<table>
<thead>
<tr>
<th>RCT</th>
<th>Study Population</th>
<th>Rivaroxaban</th>
<th>Comparator</th>
<th>Primary Efficacy Outcome</th>
<th>Rivaroxaban Event Rate</th>
<th>Comparator Event Rate</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPASS</td>
<td>Stable multivessel CAD or PAD or both and age ≥ 65 years plus a 2 vascular beds involved or 2 additional risk factors</td>
<td>2.5 mg bid + aspirin 100 mg od (n=8,313) or aspirin 100 mg od (n=8,261)</td>
<td>stroke, MI, cardiovascular death</td>
<td>4%</td>
<td>6%</td>
<td>0.74 (0.65-0.86)</td>
<td></td>
</tr>
<tr>
<td>COMMANDER HF</td>
<td>Chronic HF LVEF &lt; 40% and CAD plus BNP ≥ 200 pg/mL or NT-proBNP ≥ 800 pg/mL and worsening HF within 21 days</td>
<td>2.5 mg bid (n=2,507) plus standard care (aspirin and DAPT permitted)</td>
<td>Placebo (n=2,515) plus standard care (aspirin and DAPT permitted)</td>
<td>All-cause death, MI, stroke</td>
<td>25.0%</td>
<td>26.2%</td>
<td>0.94 (0.84-1.05)</td>
</tr>
<tr>
<td>NAVIGATE ESUS</td>
<td>Ischemic CVA (7 days-6 months) and age ≥ 49 years; no lacunae; no extracranial intracranial stenosis &gt; 50%; no embolic source + 24 hr EKG; if age 50-59 years, also had to have at least 1 additional risk factor</td>
<td>15 mg od (n=3,609)</td>
<td>Aspirin 100 mg od (n=3,604)</td>
<td>First recurrent stroke or systemic embolism</td>
<td>5.1%</td>
<td>4.8%</td>
<td>1.07 (0.87-1.33)</td>
</tr>
<tr>
<td>MARINER</td>
<td>age ≥ 40 years, plus hospitalized for 3-10 days plus stroke or MI, or a score ≥ 4 on a scale of 0-10 based on age ≥ 75, plus D-dimer ≥ 2 x upper limit of normal plus received in hospital LMWH or UFH</td>
<td>10 mg od (n=6,007) for 45d post discharge</td>
<td>Placebo (n=6,012)</td>
<td>Symptomatic VTE or VTE death</td>
<td>0.83%</td>
<td>1.10%</td>
<td>0.76 (0.52-1.09)</td>
</tr>
</tbody>
</table>

Abbreviations: bid, twice daily; BNP, brain natriuretic peptide; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; HF, heart failure; LMWH, low-molecular-weight heparin; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro brain natriuretic peptide; od, once daily; PAD, peripheral arterial disease; UFH, unfractionated heparin; VTE, venous thromboembolism.

Dr. Linkins has received data adjudication fees for the MARINER trial.
Molecular Versus Morphologic Classifications of Myeloproliferative Neoplasms: You Don't Know JAK!

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Although clinciomorphologic classification of malignancies has been the mainstay of diagnostic pathology for years, the past decade has seen a progressive trend to use molecular genetic data to inform diagnosis and prognosis, and to predict response to a rapidly evolving arsenal of therapies. In fact, hematologic neoplasms have been at the forefront of this paradigm shift that is sweeping through oncology. This deeper genetic understanding has resulted in more precise diagnostic classification (e.g., BCR-ABL1 in chronic myeloid leukemia [CML],KIT mutations in systemic mastocytosis) as well as created subclassifications that stratified patients both based upon prognosis (e.g., BCR/ABL1 deletions in B-cell precursor lymphoblastic leukemia and TP53 mutations in acute myeloid leukemia [AML]) and targeted therapeutic opportunities (e.g., IDH1/2 and FLT3 mutations in AML, BCR-ABL1 rearrangements in CML and ALL). The year 2018 saw the field undergo a new paradigm shift. Rather than refining existing clinicomorphologic categories, new molecularly defined categories have been identified in the myeloproliferative neoplasms (MPNs) that transcend the traditional classification scheme and provide a new approach to diagnosis and prognostication of these diseases.

MPNs are a heterogeneous group of clonal hematopoietic disorders unified by increased numbers of differentiated blood cells. The Philadelphia chromosome (Ph) -negative MPNs include polycythemia vera (PV), essential thrombocytopenia (ET), and primary myelofibrosis (PMF). The differentiation between these diagnoses has been largely based on clinical parameters such as blood cell counts, and bone marrow morphology. However, there can be substantial clinical and morphologic overlap between these entities, which can create clinical uncertainty due to the wide range of prognoses between and within these classifications. Currently, disease-specific risk-stratification models place patients into broad risk categories that are primarily based on cell counts, age, thrombosis risk, and limited genetic data.1 The latter include driver mutations in JAK2, CALR, and MPL that can be identified in the majority of Ph-negative MPNs. However, these mutations lead to functionally convergent oncogenic JAK-STAT signaling and do not discriminate between the MPNs.

Nevertheless, a number of other diverse pathogenic mutations that can influence phenotype and clinical outcome can also be identified in these diseases.2 Our rapidly evolving genetic understanding of MPNs raises the tantalizing possibility of building a more holistic multiparametric model incorporating high-dimensional phenotypic and genomic data that may have predictive power across all Ph-negative MPNs. To address this possibility, Dr. Jacob Grinfeld and colleagues undertook targeted next generation sequencing of exonic regions of 69 myeloid cancer genes to detect single nucleotide variants and copy number changes in a retrospective cohort of 2,035 patients with Ph-negative MPNs—the largest molecularly characterized cohort of patients with MPN.2 Thirty-three recurrent mutated genes were identified with JAK2, CALR, and MPL being the sole somatic variants in a large subset of cases (4%). Using a combination of Bayesian network modeling and Dirichlet process mixture modeling approaches, eight genomic subgroups were identified, each with distinct clinicopathologic phenotypes including outcomes (Figure 1). Importantly, the eight subgroups in many cases contained representations from all three main subtypes of Ph-negative MPNs, consistent with rethinking of traditional diagnostic categories into these molecularly-defined diagnostic groups. The recategorized groups demonstrate several recurrent principles that hold true across all myeloid neoplasms.3 For example, the subgroups with TP53 mutations and mutations involving chromatin modifying/splicing genes generally occurred in older patients with poor outcomes (relative to the JAK2 heterozygous subgroup), regardless of MPN phenotype, a pattern seen in other hematologic malignancies.

Furthermore, the authors generated a multiparameter multistate prognostic model, combining 63 clinical and genomic variables to generate a comprehensive individual survival model across all Ph-negative MPNs (access the MPN personalized risk calculator via https://cancer.sanger.ac.uk/mpn-multistage/). The model showed high predictive accuracy in internal cross-validation of a training cohort and in an independent external validation cohort. The resultant prognostic model consistently outperformed the International Prognostic Scoring System (IPSS), the Dynamic IPSS (D-IPSS), as well as high molecular risk category for myelofibrosis and the International Prognostic Score for Essential Thrombocytopenia (IPET). Again, clinical and molecular data predominated the prediction algorithms for progression to myelofibrosis, AML, and death (Figure 2), while traditional morphologic subtype did not. For example, age was the single most powerful predictor of death, while it was relatively less important in predicting progression to AML or myelofibrosis. Conversely, cell counts and genetic factors played a dominant role in predicting the latter. By contrast, the MPN subtype provided only a modest contribution to predicting progression to AML and did not significantly contribute to other state transitions. These findings collectively underscore that the distinction between chronic-phase disease such as ET and PV and myelofibrosis (including both PMF and post-PV/ET myelofibrosis) improved predictive accuracy of the model, the distinction between ET and PV did not improve accuracy. These findings collectively suggest that, at least for multiparameter prognostication using clinical and genomic data, the distinction of certain traditional diagnostic categories (ET vs. PV) may be dispensable.

This study raises the philosophical question regarding the future utility of the conventional classification system of MPNs, and indeed all neoplasms, that relies upon morphologic features with only limited utilization of genetic data. In the case of MPNs, the traditional diagnostic categories has also been challenged in the lymphomas. The results of genomic characterization of large cohorts of diffuse large B cell lymphomas (DLBCL) were published consecutively by two separate groups (also reviewed in the September/October 2018 issue of The Hematologist this year by Drs. Caron Jacobson and Andrew Roberts). Like MPNs, DLBCLs are a heterogeneous group of tumors with variable clinical behavior that may be partially predicted using conventional prognostic models. Dr. Bjorn Chapuy and colleagues (as well as Dr. Roland Schmitz and colleagues)5,6 have identified molecular subtypes of DLBCL that were distributed across conventional germinal center-like (GCB) and activated B cell-like (ABC) subgroups but provided prognostic information independent of Cell-of-Origin and IPI classification. Analysis of MPNs, both in the current study and others, offer proof-of-principle that genomic profiling can offer orthogonal prognostic information.

The identification of molecularly defined diagnostic categories that transcend traditional classification schemes in no way suggests that clinical and morphologic information is not needed. However, the findings of the past year have emphasized the added value of such a broader multidimensional approach that synthesizes clinical, morphologic, and extensive molecular genetic data (including somatic, copy number, and structural variants) in support of clinical decision-making. The dimensionality of the data is so vast that simple algorithms will no longer be sufficiently granular. Online "calculators,” such as that provided by Dr. Jacob Grinfeld and colleagues, will be required to generate patient-specific diagnostic information. So, while 2018 has been the year of broad molecular diagnostic data, let 2019 usher in the exciting and challenging task of translating these rapidly evolving insights into robust ancillary tools to enrich traditional diagnostic categories and fulfill the promise of precision medicine across all hematologic neoplasms.

The Hematologist with historical controls, improved the CR rate and two-year PFS in CLL to 51 percent and nonoverlapping toxicity profiles. In an early-phase study, this combination, when compared both CLL and MCL, the potential use of these combinations in earlier lines of therapy, and the single agent in the multiply-relapsed setting, this year has seen an expansion of the role of including inhibition of the B-cell receptor pathway. On the heels of the clinical success of the treatment options for patients with CLL and MCL who have exhausted other therapies cell lymphoma (MCL) with 75 percent of patients responding and 21 percent of patients percent across a variety of different diseases. Responses were significantly greater in mantle lymphoma (B-NHL) were also favorable, though not as promising, with a response rate of 44 and were equivalent in high-risk del(17p) patients. The persistent investigation into inhibiting BCL-2 despite a lack of initial success has been very fortuitous for patients with B-cell malignancies, especially high-risk CLL and MCL, two incurable diseases with limited treatment options and relatively short OS. The discovery of the potent and specific BCL-2 inhibitor venetoclax with its favorable toxicity profile and high response rates as a single agent in these diseases has provided additional options for patients. This year dovetailed on the initial success of this drug and identified two new, highly effective combination partners, rituximab and ibrutinib, to move into the clinic, resulting in able to offer time-limited therapy with what seems to be an improved safety and tolerability profile is highly appealing. In MCL, there is even more room for improvement with combination strategies over single-agent venetoclax. As with venetoclax-rituximab, the observed preclinical synergies and lack of overlapping toxicity of dual BTK and BCL-2 inhibition led to a phase I study of venetoclax in combination with ibrutinib. Twenty-four patients were enrolled, treated with a median of two prior therapies; one patient was treated in the first line due to a chemotherapy contraindication. Three quarters of patients had high-risk disease by the MCL International Prognostic Index and half of the patients had alterations involving TP53. One patient had the blastoid/pleomorphic variant. CRs including positron emission tomography (PET) imaging were seen in 71 percent of patients, and 67 percent of patients were found to be MRD negative by flow cytometry. Estimated PFS at 12 and 18 months was 75 percent and 57 percent, respectively. The most common adverse events were diarrhea, nausea, and vomiting, but most were low grade. Responses were seen despite adverse prognostic factors, although a Ki-67 index of at least 30 percent was associated with an increased risk of nonresponse. Targeted sequencing was done on tumors from all patients; patients with mutations associated with BTK inhibitor resistance did respond (CR, 83%), as did patients with alterations in TP53 (CR, 56%). Based on these promising results, a randomized trial of venetoclax-ibrutinib versus ibrutinib alone could be useful earlier in the disease course, hopefully changing their natural history. The question of how to overcome many adverse prognostic factors and resistance mechanisms to single agent therapy, and lead to MRD negativity in most patients. This translates into improved response duration and in the case of CLL, improved OS as well as the opportunity to offer time-limited rather than indefinite therapy. These two studies and these two combinations will undoubtedly benefit many patients and spur investigation of additional combinations that could be useful in earlier disease course, hopefully changing their natural history.

Expanding the Role of Venetoclax: Mantle Cell Lymphoma and Chronic Lymphocytic Leukemia

C. Jacobson, MD

Caron JACOBSON, MD

Leukemia


Deciphering the Dilemmas Posed by Detection of Mutant Myeloid Clones

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The explosion of next-generation sequence analysis (NGS) in the last five years has provided major new insights into the biology of acute myeloid leukemia (AML) while posing new dilemmas for hematologists in both the laboratory and the clinic. Two discoveries have been particularly confronting. First, healthy older people with normal blood counts often can harbor myeloid clones bearing mutations in AML-driver genes — so-called clonal hematopoiesis of indeterminate potential (CHIP) — as reviewed by Drs. Joanna Conant and Tracy George in the January/February 2018 issue of The Hematologist.2,3

Second, many AML patients in first remission have persisting clonal hematopoiesis-bearing mutations in AML-driver genes, as discussed by Dr. Annette Kim in a July/August 2018 Diffusion article.4 These discoveries pose the obvious question of what the detection of mutant myeloid clones means for health and whether all clones have similar significance.

This year, major advances have been made in deciphering these questions in the context of healthy individuals with no history of blood disorders, and two articles are equally worthy of being listed as the year’s best. Dr. Sagi Abelson and colleagues5 and Dr. Pinkal Desai and colleagues6 tackled the challenge of defining the risk of developing AML when mutant myeloid clones are detectable in healthy people. Dr. Abelson and colleagues identified 95 individuals with blood samples suitable for sequencing an average of 6.3 years before AML diagnosis (pre-AML group) and compared their mutational profile with that of 414 age-stratified and sex-matched controls. Dr. Desai and colleagues performed deep sequencing of serially collected peripheral blood samples obtained from 212 women a median of 9.6 years before their diagnosis of AML along with 212 age-matched controls. Reassuringly, the results of both studies are mutually consistent and informative.

Compared to controls, patients destined to develop AML were more likely to have a detectable mutation in an AML-driver gene (odds ratio, 4.86 in Dr. Desai and colleague’s study) extending previous data that indicated a higher risk of developing myeloid malignancy, but not AML specifically, for people with CHIP. However, CHIP was common in controls, especially in those older than 65 years (odds ratio, 5.19 in both studies), and AML was rare, meaning that most people with CHIP are not destined to develop AML. To address this, both studies refined their analyses, focusing on comparisons between people with pre-AML and controls who had CHIP. They identified that AML risk increased as the number of mutations increased, as clone size (measured as variant allele frequency [VAF]) increased and if the driver mutations were in specific genes, particularly TET2, splicing factors (e.g., U2AF1, SF3B1), DNMT3a, and TET2, and, in Dr. Desai’s study only, BMY, HM, and SFB1 (Figure). TPS3 mutations conferred the highest risk when genes were considered in isolation. The most commonly aberrant CHIP-defining genes, DNMT3a and TET2, were associated with heightened risk of progression to AML as single abnormalities, but most healthy people with these mutations as single mutations did not progress to AML. The risk was much greater when more than one variant was detected and when DNMT3a mutations co-occurred with a splicing gene mutation. These two studies now allow identification of people with CHIP who are at highest risk of subsequently developing AML. Importantly, they teach us that when assessing a person with CHIP, the details allow identification of people with CHIP who are at highest risk of subsequently developing AML, but most healthy people with these mutations as single aberrations did not.

DNMT3a

As Dr. Roberts pointed out, the size of the mutant clone was important. Therefore in the context of AML in first CR, the clinical importance of detecting a persisting mutant myeloid clone pivots on which gene or genes are mutated. As in the case of CHIP in healthy people, the presence of a clone with a single mutation in DNMT3a or TET2 seemed compatible with a favorable outcome in the first three years of follow up.

Collectively, the findings of these articles provide valuable clues as to how to assess what a mutant myeloid clone means for a specific patient. The gene(s) affected, the number of mutations, the size of the clone, and clinical context, all need to be considered together.

2. Kim AS. The usual suspects aren’t the bad guys! Molecular MDR comes of age in AML. The Hematologist. 2018;15:4

From Aminopterin to Tisagenlecleucel: Childhood Acute Lymphoblastic Leukemia at the Forefront of Cancer Breakthroughs

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Prior to the 1940s, acute lymphoblastic leukemia (ALL) was universally fatal. More than 50 years ago, Dr. Sidney Farber developed the concept that a mutualist antitumor aminopterin could induce remission in children with ALL.7 This seminal finding established that cytotoxic chemotherapy can kill cancer cells. Year by year, pioneers such as Drs. Gertrude Elion and George Hitchings, Emil Frei, Don Pinkel, and others, successfully demonstrated improvement in care for these children, and today, approximately 90 percent of children diagnosed with ALL are cured.8-11 ALL has been long been the vanguard for novel anti-neoplastic approaches.

Yet, even in pediatric ALL, not all children respond to treatment, and the short- and long-term adverse effects of therapy can affect health and quality of life significantly. Immunotherapies have the potential to improve outcomes with reduced adverse effects because of nonoverlapping toxicities with conventional cytotoxics, and 2018 saw gratifying developments in the application of these new agents.

The three main types of immunotherapies that have been used to treat ALL successfully are monoclonal antibodies (e.g., rituximab), bi-specific T-cell engagers (BiTEs), and chimeric antigen receptor engineered T cells (CAR-Ts) — arguably, the most groundbreaking immunotherapy to be studied in ALL.12 As readers well know, CAR-T therapy involves genetic modification of T lymphocytes to express artificial receptors that can target surface antigens. CD19 is an ideal target for immunotherapy, especially with CAR-Ts. CD19 is found only on normal and malignant B cells and not on other tissues or organs, and is important for early-stage B-cell development, growth, and survival. The concept of using T cells to target malignancies was pioneered by Dr. Stephen Rosenberg and colleagues in the 1980s.13 Early trials using CD19-targeting CAR-T were largely unsuccessful because of T-cell anergy resulting in poor proliferation and persistence, due to a lack of co-stimulation. These first-generation CAR-Ts only contained a cytokine domain and antibody-based external receptor. Second-generation CAR-Ts added T-cell co-stimulatory signaling domains such as 4-1BB or CD28, which have led to robust antitumor responses in preclinical models and patients.

Tisagenlecleucel (CTL019) is a CD19-targeting CAR-T developed in collaboration between the University of Pennsylvania (UPenn), Children’s Hospital of Philadelphia (CHOP), and Novartis Pharmaceuticals. This CTL019 product contained a CAR bearing the 4-1BB co-stimulatory domain, which was subsequently established to be highly effective in children with r/r B-ALL.14-16 Similar observations were confirmed by others.17-19 The product bearing the CD19-targeting, 4-1BB co-stimulatory domain was approved by FDA in 2017 and EMA approval in 2018 based on the results of the EJLANA trial.20 This study was a phase II, single-cohort international trial that treated more than 70 children and young adults with r/r B-ALL with a single infusion of tisagenlecleucel. In this refractory patient

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In summary, from the first use of cytotoxic chemotherapy to the FDA approval of a gene therapy, childhood ALL has been at the forefront of new treatment breakthroughs for 80 years. Population, the overall remission rate at three months was 81 percent, and the 12-month EFS and OS were 50 percent and 76 percent, respectively. All patients who achieved CR were cured of their disease, with a median follow-up of 80 years.

In summary, from the first use of cytotoxic chemotherapy to the FDA approval of a gene therapy, childhood ALL has been at the forefront of new treatment breakthroughs for 80 years. Population, the overall remission rate at three months was 81 percent, and the 12-month EFS and OS were 50 percent and 76 percent, respectively. All patients who achieved CR were cured of their disease, with a median follow-up of 80 years.
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15  ASH Physician-Scientist Career Development Award application due  
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15  ASH Research Training Award for Fellows application due  
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18-19  Highlights of ASH in North America  
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    New York, NY  
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25-26  Highlights of ASH in North America  
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February

1  ASH Latin American Training Program application due  
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